Karen Kattai
University of Toronto
Library
Serials Dept.
Robarts Bldg. U. of T.

MEDICAL JOURNAL

UNIVERSITY OF TORONTO

VOL. LIX.
NO.4

Digitized by the Internet Archive
in 2018 with funding from
University of Toronto

https://archive.org/details/medjournalMay1982uoft

P82-0193 1681

MEDICAL JOURNAL
UNIVERSITY OF TORONTO

Established December 1923
An Undergraduate Publication

Volume LIX, Number 4
May 1982

CONTENTS

Editorial: **The Written Word.** *Davy Cheng* 114

Feature: **Half a Century of Histology: Profile on Harry Whittaker.** *Dele Davies* 115

Biomedical Engineering: **Mechanism of Synthetic Polymer Bioadhesions.** *M.J. Bazos and P.Y. Wang, Ph.D.* 118

Cardiovascular Research: **Validation Studies of a New Model of Myocardial Perfusability.** *David Malkin and Colin Bayliss, M.D.* 121

Clinical Biochemistry: **Biochemical Aspects of Plasminogen Activator and its Possible Role in Metastatic Neoplasms.** *Raymond Ng and Andie Lam* 124

Gastroenterology: **Gastrointestinal Endoscopy: The Past and Future.** *Paul Boughen* 129

Haematology: **Chronic Myelogenous Leukemia.** *Charles Whelton* 135

Medical Ethics: **The Medical Student's Niche in the Hospital Setting: What Price Education?** *Richard Hegele* 139

Public Health: **Water Fluoridation.** *Anne Curtis* 141

Commentary: **On the Importance of Creativity in a Medical Education.** *Harley Hahn* . . . 147

Medical Alumni: **The U. of T. Medical Alumni Association.** *B.I. Giblon, M.D.* 149

Medical Education: **An Experiment in Ethics.** *Paul Ferner and Peter Singer* 151

Editor-in-Chief . . . . . Davy Cheng M.Sc. 8T3

Associate Editors . . . . . Paul Boughen 8T3
Michael Dan 8T4
Peter Singer 8T4

Advertising Director . . . . . George Vincent 8T3

Journal Staff . . . . . James Chu 8T3
Robert Jin 8T2
Robert Kyle 8T3
Anne Summers 8T2
Raymond Tong 8T3

Cover Illustration . . . . . Mary Trafford AAM 8T3

GUIDELINES FOR PUBLICATION

1) All articles intended for publication should be submitted to the editors before the deadline which is usually six weeks before the release of the Journal.
2) Submitted articles should be typed (or legibly printed) double-spaced, single-sided on paper 8 1/2" x 11" (letter size) and they should not be more than 15 to 20 pages (3000 to 4000 words).
3) Illustrations, graphs, diagrams and figures should be put on a separate sheet and identified by Arabic numerals. A list of explanatory legends for all the figures and diagrams should be put on another sheet. Do not write on the back of photographs.
4) References should be checked with the original sources, designated by raised Arabic numerals in the text, and listed in alphabetical order on a separate sheet. Each periodical reference should include in order: the author's last name and initials, title of the article, journal name, volume number, page number, and year (e.g. Risser JC: Scoliosis: Past and Present. *J Bone and Joint Surg* 46 (A): 167, 1964). For further information please consult the MLA Stylesheet.
5) The editors reserve the right to make such editorial changes as are deemed necessary to ensure correctness of grammar and spelling, clarification of statements and conformity to Journal style.
6) Acceptance for publication is subject to the understanding that such material is submitted solely to the Journal and will not be reprinted without the consent of both the editors and author.

The Written Word

On closing with this final issue of the *University of Toronto Medical Journal*, Volume LIX, I would like to re-emphasize the essence of communication. These have always been the aims of the *Journal* to convey information of academic and clinical interest to undergraduate medical students and to act as a forum in which students can develop and refine their skills as scientific writers.

In our present computer age of scientific training, multiple choice examination becomes part of our life. Surely, it provides a more objective assessment of student's knowledge than an essay-type examination which requires, in addition, his ability to communicate. However, we may have sacrificed an essential art in conveying information.

A doctor has to communicate not only with his colleagues, but he must also be able to do so with his patients and the community. Communication is not merely a superficial or sometimes confusing display of information, but an earnest attempt to ensure that the meaning and significance are clearly comprehended. This is particularly important in the preparation of scientific articles and lectures.

It is a matter of pride and satisfaction that the *Medical Journal* has provided a stimulus for students to express their interests and efforts in writing. And, in order to continue to provide this high calibre of writing to our readers, I would encourage more of our undergraduates to avail themselves of this opportunity for communication.

Finally, I would like to express my sincere appreciation to the associate editors, Journal staff and advertising director, who have given generously of their time and inspiration over the past year. In addition, my appreciation goes to Mrs. A. Randall for her excellent secretarial help.

My congratulations also to this year's authors for the fine articles they produced. In particular, I gratefully acknowledge my appreciation to Dr. F.H. Lowy, Dean, Faculty of Medicine, University of Toronto and Dr. H.W. Henderson, Deputy Registrar of the College of Physicians and Surgeons of Ontario for their generous guest editorials.

I wish to thank the Medical Society, advertisers, subscribers and patrons for their kind support. Special thanks also to the students of the Art as Applied to Medicine Department whose skillful talents added so much to our publications. In addition, I would like to extend my thanks to Collier Macmillan Canada, Inc. for their supply of new books to the *Journal* for review.

Lastly, I would like to acknowledge the fine typesetting and printing work of Ms. I. Rudd of Media I Graphics and Mr. M. Lee of Metrospan.

My association with the *Journal* has indeed been both challenging and rewarding, and I wish the editors and staff every success in years to come. □

Davy Cheng 8T3

Half a century of Histology: Profile on Harry Whittaker

Dele Davies 8T5

September 1974. A new laboratory instructor arrived at the Medical Sciences Building for the first time. Confronted with its size, she loitered around the lobbies for a while before finding a place where she patiently waited. Plaguing the back of her mind most of all was how she would cope with the notorious impersonality of a big university.

Not to worry. Before very long Harry found her. As she recalled, "I vividly remember this man wearing a white coat and a warm friendly smile, coming up to me, shaking my hand and saying: 'Hello, you must be Mrs. Akesson. My name is Harry. I was expecting you. Welcome to the Department. I'll take you over to where the other instructors are having a meeting' ". That certainly made her day.

Harry Whittaker was born in 1913 in Liverpool, England, and moved to Canada with his family when he was just six weeks old. His family settled in Toronto, where he grew up and attended Central Technical School. He graduated in 1929, and joined the Histology Department at the University of Toronto in 1930 at age sixteen. He married Violet Clark in 1938, and has one son, born in 1945, who holds a PhD in English Literature.

When Harry joined the Histology Department in 1930 he worked as a technician under Professor Piersol. His early years were spent at the Old Medical School, now the McMurrich Building, preparing slides and learning to deal with the 150 odd medical students that made up the First Year class. Among these students was a Dr. Chute who later became Dean of Medicine in the new Medical Sciences Building. Well, Harry has come a long way since that first year, and has known or instructed over 50 classes of medical students, many of whom have gone on to very distinguished careers.

However, Harry himself has not really changed. According to Dr. Colin Bayliss — an ex-student of Harry's some twenty-five years ago and now himself a popular lecturer in physiology — "He's the same guy now as he was then. I knew him in 1957 in the old Anatomy Building. At that time we had to purchase our own microscopes for about $100. He fixed a little hair marker into the eyepiece of my microscope. He would go around to all the students, checking to see if we had drawn a cell or an eyelash — we had to draw our slides in those days. He always cared for the students and still does. He was just as famous then as he is now. Sure, histology has changed tremendously in the last 25 years, but Harry Whittaker? No, thank God he hasn't".

Harry Builds Ham a Camera

When the famous Dr. Ham moved to Toronto in 1932, it meant for Harry the start of a very close relationship that persists until the present. Dr. Ham recalls: "In 1932 I was in St. Louis when I was asked by the late Dr. J.C.B. Grant to take over the Department of Histology at the University of Toronto. All we had in those days were the student's microscopes, and no oil immersion lenses. I took on a young student as a technician, and for many years both of us taught the Histology course together. That young man was Harry. In 1947 when I was writing the first edition of my book we didn't have much in the department in the way of equipment, so Harry built a home-made camera and took some of the photographs that went into that book. We really had a lot of fun together, and we were the only two people in the Department for many years, until we were joined by other staff as the Department expanded. He's one of the nicest persons I've known over the years, and we are very good friends to this day".

Keep things simple

Harry had an insatiable desire to learn from the great teachers around him, especially when it came to tricks that improved his relationship with the students. Thus, from the late Dr. Grant he picked up the habit of gracefully calling all medical students 'doc'. And from Dr. Ham he learnt this invaluable piece of advice, which he now passes on to the students: "Keep things simple. Learn the basics whatever you're doing so that you have something to build on." Any medical student who has attended U of T in the past 50

years is probably familiar with the stream of Harry analogies such as 'chicken wire' (adipose tissue), 'Swiss cheese' (bone or cartilage), 'golf ball on a tee' (Graafian follicle), and the list could go on forever. Probably favourite of all is the now famous 'pits and glands' (gastric mucosa) song frequently chanted at his ever-popular lunchtime reviews.

Future Patients

Needless to say, Harry has had a lot of experience in dealing with other people. He may be regarded as the thread linking together generations of faculty members, and the yearly crop of medical students. Apart from his dealing with medical students, Harry recalls various jobs he previously had, and how important it is to meet people from every walk of life. He worked for one year at a Goodyear rubber factory of which he had this to say: "Working in a factory is something everyone should have a go at. It's a valuable experience even for medical students, as you will meet the people that will one day form the core of your practice. It's enlightening to meet people like these — shocking sometimes — especially to people who have lived a sheltered life. However, you get to learn a lot from them that you would not know otherwise, and will find that they are basically very good people."

Although there are many more students now than in earlier days, Harry finds that first year students are the same as they have always been. "What really bothers me about first year students is that they tend to think that because of the size of the class, they are just another number. This is not really true. By the time you get to Second Year, you will realize that we in the faculty are quite aware of you as an individual. In relation to this, I would advise students to remember when you are in practice that you are dealing with human beings, and not just numbers. Being on the other side of the fence, I think that this is a layman's chief complaint today

about doctor's attitudes. For example, 'what's with that chronic bronchitis patient in ward A?'" However, Harry is quick to maintain that "Our graduates are second to none — they always have been".

A Frightening Experience

Harry realizes that with people coming to big universities for the first time reassurance can go a long way: "It's a frightening experience. It doesn't cost you anything to reassure people. Stop and say hello and make someone feel good. The reason why students find it easy to approach me is because I am not considered an authority figure, but as one of you. However, I feel that this is a very wrong attitude. Students should learn that the staff are not unapproachable and they will invariably find that they care too. I think that the students that are having difficulties are misdirected — they can't blame their capacity to learn or else they wouldn't be in medical school. Somehow they must lack organization. I've always believed that everybody assimilates what they are told the first time, but the problem is in recall. I would like to use the term 'follicle' as an example. If someone says the word 'follicle' to you, you should immediately have a recall of what it is histologically, and how many types of follicles there are. It's a logical thought process — no use searching for the trees if you haven't found the forest. I think that this principle could be

applied to any of the basic sciences, or to your clinical work. I have found that kids that excel here usually have a marvellous degree of organization."

Bottoming Chairs

Away from work, Harry has numerous interests including photography, major league baseball, and reading detective novels. However, his greatest desire is for 'bottoming chairs', which in plain English means relaxing and thinking about life in general as it is going on about him. He is genuinely concerned about certain aspects of life as he sees them, especially when it comes to medical students and practicing physicians.

"Perhaps the biggest problem among kids today is that they have so many opportunities and freedom of choice. In my case it was a job — either work or don't eat — pure economic sense. Freedom of choice creates problems — after deciding what they want to do, many people spend the rest of their lives wondering if they made the right decision. I often meet doctors in their intern years and they are frequently very bitter and unhappy about their careers. They think they've taken the wrong turn. This really bothers me because I know they are on the right track. There has to be a reason why they opted for this vocation, and I'm sure if they did anything else they would probably be unhappy. I think that if you are stuck with a job and there are no real alternatives, whatever it may be that you're doing, be happy with it. Otherwise you're going to be up the wall. This happens occasionally with doctors."

Not Suited for Medicine

Harry never really wanted to become a doctor. "I like people a lot, but I never thought I was suited for medicine." The highlights of his career — "many", but mainly in 1975 when he was nominated by the students, and received the Ontario University Teaching Award — "particularly because it was initiated by the students themselves. It meant a lot to me". Lowpoint: student's rebellion in 1969, "...when we first moved into the new building. It began in the United States, and was really a rebellion against authority. Youth generally tend to go along with the mood of their times."

Histology? No — But How is Harry?

Many students and faculty members had a lot to say about Harry.

Dr. D.L. McLeod, professor of anatomy (ex-Harry student, now colleague): "Over the years I have learnt that the name Harry Whittaker is synonymous with histology. I am constantly amazed by the number of U of T medical graduates who, having forgotten their histology, still remember the name Whittaker and ask with affection: 'and how is Harry?'"

Dr. A. Roberts, assistant professor of anatomy (ex-Harry student, now colleague) thinks "...he's probably the best instructor you'll ever get. A real fountain of knowledge. I learnt an awful lot from him. He's also very modest."

Dr. A.A. Axelrad, professor of Anatomy and head of the Division of Histology: "He is a very special mix of the great teacher who is always trying to convey complex ideas simply and then sparing nothing to make sure that the ideas got across, the old friend who always has a new joke to tell, and the gentle, caring human being who thinks hard about his students while they are with him and remembers them long after they have gone. I cannot imagine the course without him and will do everything in my power to make sure he has the opportunity to continue Harrying the students just as long as it is humanly possible."

Dr. K.L. Moore, professor and chairman of the Department of Anatomy: "He's an outstanding teacher. He's into post retirement now, but we've been most anxious to try and keep him on. We'll continue to try as long as he is willing to stay and help the students."

Dr. W.M. Brown, associate professor of anatomy: "Histology would certainly suffer if he wasn't there. He has been father to numerous generations of students, and always has plenty of time for everyone."

But how do present students feel? Relax. An informal survey of the First, Second, and Third Year classes confirmed that Harry Whittaker led the queue. Sure, times have changed, but it's good to know that *our* Harry's beat goes on and on.

Acknowledgements

The author would like to thank the following people for their generous time and cooperation: Dr. A. Ham, Dr. C.E. Bayliss, Dr. D.L. McLeod, Dr. A. Roberts, Dr. A.A. Axelrad, Dr. K.L. Moore, Dr. W.H. Brown, Mrs. Akesson, and of course, Harry Whittaker.

Mechanism of Synthetic Polymer Bioadhesions

M.J. Bazos, B.Sc., 8T5
P.Y. Wang*, PhD.

The effect of various monofunctional compounds on the adhesiveness of polyurethane prepolymers has been studied using a rat subcutaneous tissue model. Benzoyl chloride was found to be the most effective in enhancing the adhesive effects of the prepolymer, as well as a number of commercially available adhesives. A mechanism of polymer - surface interactions and bioadhesion consistent with established chemical and physical laws has been proposed.

Clinical Relevance

1. Commerciaiiy available adhesives (as opposed to traditional clipping methods) have been proposed in the surgical management of berry aneurysms of the cerebral vasculature.

2. Orthopedic prosthetic devices (eg. surgical hip replacement) have long employed adhesives at the tissue transplant interface.

3. Almost one half of all Canadians over 25, and 90 per cent of our elderly require full or partial dentures. Prosthodontists and oral surgeons here in Toronto are currently exploring the possibility of replacing conventional dentures with surgically implanted tooth root substitutes.

4. Swedish scientists have found light metal titanium implants (MW. 47.9) to be very compatible with human tissue, exhibiting minimal host rejection.

5. Indeed, whole tissue integrated prosthesis may provide a new dimension and even alternative to certain types of microsurgery.

Introduction

Recognition processes in biological systems involve polymer — surface interactions of great complexity. In the field of embryology, the developmental phases of cleavage, gastrulation, and organogenesis all share in their individual abilities to acquire physicochemical structures and properties which enable them to perform their respective physiological functions. In addition, the activation of the immune system involves the recognition of polymer characteristics unique to a particular antigen, and presents one of the least understood and hence intriguing areas of biomedical research.

The complexity of biosurfaces, coupled with inadequate experimental design, and a generalized lack of understanding has led to ambiguous and often contradictory results in many studies of the interactions involving cells and their surface macromolecular components. For example, earlier work on cell adhesion onto solid surfaces failed to take into account preadsorbtion of cellular protein[1 2 11]. These shortcomings have placed bioadhesion in a unique class of biological phenomena, and have led some early workers to question the conformity of bioadhesion to established physical laws.

Two problems encountered in the study of polymer — surface interactions and bioadhesion are 1) the nature of the interfacial forces at a molecular level, and 2) their effect on joint performance. Conventional testing procedures such as those used in examining adhesions between solid surfaces (eg. metal-plastic-plastic-glass, etc.) are facilitated by the well-established chemical and physical nature of these surfaces. Furthermore, certain surface characteristics (eg. roughness, cleanliness, etc.) may be readily altered to optimize selective criteria (eg. strength, durability, compatibility, etc.) Spreading or priming agents, such as alkali treatment of Teflon® before expoxy bonding, can increase contact between the surfaces to be bonded. As well, compressive forces may be applied to further facilitate intersurface contact. Finally, the extent of polymer — surface interations may be assessed to some degree by the magnitude of tensile forces required to overcome the adhesion. However, unlike the non-biological case, biosurfaces are dynamic entities which may actively adsorb, or endo-and exocytose a host of molecules. Individual cells which are components of a biosurface vary in size, number and type of pseudopodia, microvilli, and surface molecules. Hence, they are not easily defined on a chemical and physical basis.

This report briefly describes certain synthetic polymer adhesions which provide insight into polymer-surface interactions within the biological system.

* *Laboratory of Chemical Biology, Institute of Biomedical Engineering, Faculty of Medicine, University of Toronto, Canada, M5S 1A8*

Material and Methods

On Surgical Tissue Adhesive

Chemical Coupling Agents: Conventional polymer adhesives were obtained from commercial sources[4 5 10]. In addition, a polyurethane prepolymer was prepared from the highly reactive 6-chloro-2,4,5-trifluoro-1, 3-phenylene diisocyanate (4M), castor oil (1M), pyridine (1M) and trace amounts of other additives[5]. Benzoyl Chloride and other reactive monofunctional organic compounds (Table I) were purchased from several Chemical Suppliers. The alkyl cyanoacrylate monomer liquids were received as gifts.

In Vivo Adhesive Testing: Male Wistar rats weighing 320 - 480 g were kept in separate cages and given a standard diet and water *ad libitum*. Operative procedures were performed under sodium pentobarbital anesthesia (1.0 ml/kg i.p.) in accordance with the Animals for Research Act of Ontario.

Adhesion tests were conducted using the dorsal skin tissue. Briefly, the procedure involved the incision of dorsal skin in full thickness, followed by the application of a bonding adhesive system over the exposed tissue surface. The pressure required to disrupt the incision closed by the particular adhesive mixture was recorded on a pneumatic tensiometer[5 9 10]. Rats within a body-weight range of 320 - 480 g gave reproducible measurements as their skin thickness was essentially similar. Another method[9] employed the surface of the liver for adhesion measurements.

Results

On Polymer Adhesion to Biological Tissue

The fast setting polyurethane prepolymer prepared from perfluorodiisocyanate, showed negligible adhesion to the subcutaneous tissue[5]. However, when monoisocyanates with increasing alkyl chain-length were mixed with the prepolymer, the adhesion onto tissue increased and reached a maximum for the n-hexyl derivative[7]. This same result was obtained when the tissue surface was primed with n-hexylisocyanate instead of adding it to the prepolymer adhesive; whereas n-hexylamine was found to be ineffective. Other monofunctional reactive compounds (Table I) also showed various degrees of improving the adhesion; but, their hydrolysis products were again ineffective. Benzoyl Chloride was the most effective; and, when primed onto the surface of the tissue, or mixed with several common industrial adhesives (Table I), it readily induced adhesion onto the subcutaneous tissue.

TABLE I

Improvement in Adhesion of the Polyurethane Prepolymer by Various Monofunctional Compounds

Monofunctional * Compound Added	Structural Formulae	Molecular Weight	Adhesion (gauge reading, psig)**
None			4.0
Methyl cyanoacrylate	$C_2C{=}C(CNE)\text{-}CooCH^3$	111	7.8
Phenyl isocyanate	$C_6H_5\text{-}N{=}C{=}0$	119	8.7
n-Hexyl isocyanate	$C_6H_{13}N{=}C{=}0$	127	10.6
Benzoyl chloride	$C_6H_5\text{-}COC1$	140	14.0
Tolylene Diisocyanate	$CH_3C_6H_4(N{=}C{=}0)_2$	175	10.0
Toluenesulfonyl chloride	$p\text{-}CH_3\text{-}C_6H_4\text{-}SO_2C1$	206	9.7
Triphenyl chloromethane	$C\text{-}(C_6H_5)C1$	278	9.5

* Added in the amount of 1M with respect to the other components in the fast-setting polyurethane prepolymer.
** On the same scale, the strength of a similar wound healed naturally (i.e. closed by suturing) after 9 days, was 10.0

Discussion

Although the chemical structure of biosurfaces is not completely known, the chemistry of certain synthetic polymers are well established. Therefore, by studying the influence of various synthetic polymers a mechanism for bioadhesion was deduced. Among the reactive compounds studied, alkyl-cyanoacrylates were found to polymerize and adhere strongly to internal tissue. However, this compound polymerized too rapidly to allow for the manipulation of any other parameters. Consequently, a conveniently fast-setting (about 5 min) polyurethane prepolymer was prepared exhibiting negligible adhesion to biological tissue[4]. This separation of setting time and adhesion variables permitted the evaluation of 1) priming the tissue surface with low molecular weight componds, or 2) directly mixing the prepolymer with the adhesive (Table I). Among all the reactive monofunctional compounds studied, benzoyl chloride and its derivatives were found to be most effective[10]. This effectiveness is attributed to the modification of the hydrophilic tissue surface (Step 1, Fig. 2) by the hydrophobic benzoyl group (Step 2, Fig. 2) attached to tissue after reaction (Step 3, Fig. 2). The prosthetic benzoyl group makes the tissue-polymer interface more compatible (Steps 4 and 5, Fig. 2) and this results in stronger adhesion (Steps 6 and 7, Fig. 2). Most organic adhesives are prepared from high molecular weight hydrophobic polymers chosen for strength and resistance to moisture during service conditions. Naturally, these hydrophobic polymer adhesives cannot displace the water layer on living tissue and interact directly with the substrate tissue components to effect adhesion (Steps 2 and 3, Fig. 1). Thus, the adhesive and substrate are easily separated when subjected to tensile forces (Steps 3, 4, and 5, Fig. 2).

These studies on surgical tissue adhesives have demonstrated the applicability of conventional explanations based on established physical and chemical laws. The results suggest that adhesion onto a biosurface is actually a composite of two events: first, an effective coupling reation must precede the solidification of a cohesive (polymer) matrix (i.e. surface contact is the most important criterion for adhesion). Secondly, no chemical reaction is necessary between the coupling agent already attached onto the biosurface and the polymer system. Proper orientation of the coupling agent before reaction is an important feature in assessing effective coupling with available groups on a biological suface[7].

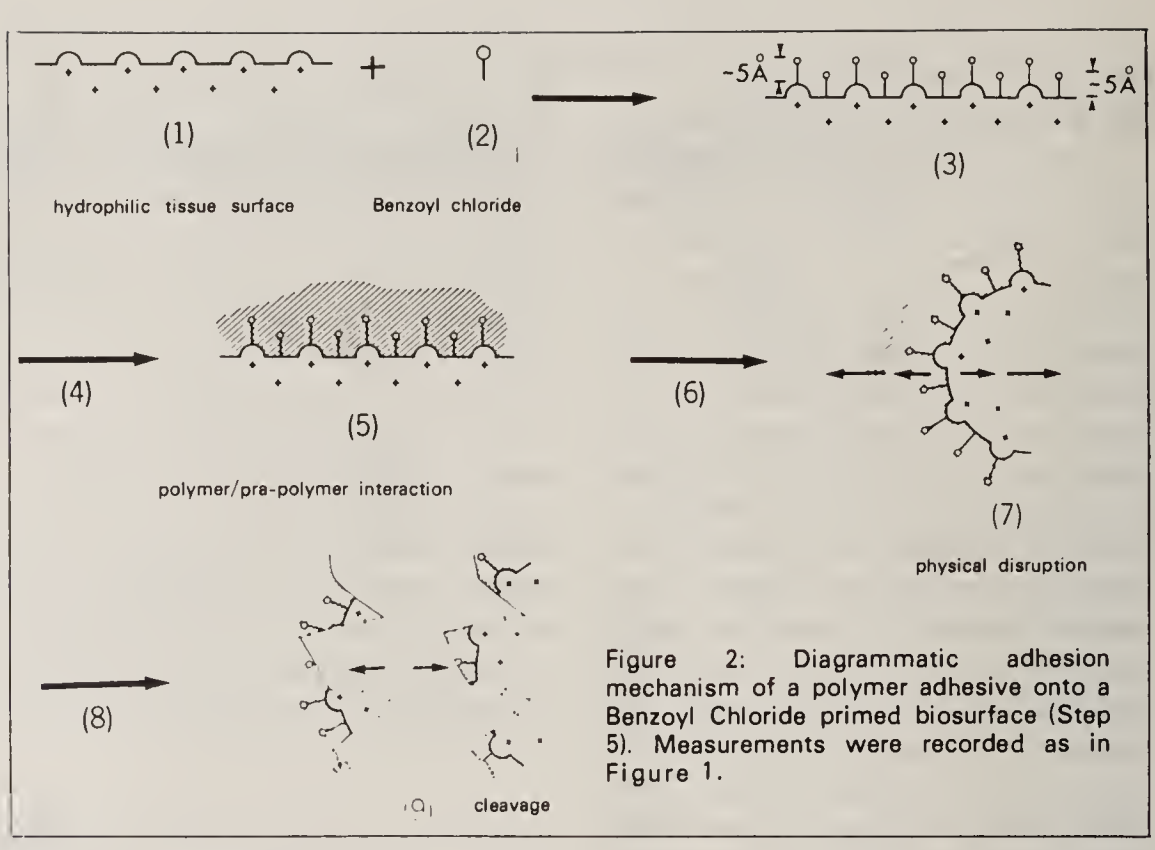


Figure 2: Diagrammatic adhesion mechanism of a polymer adhesive onto a Benzoyl Chloride primed biosurface (Step 5). Measurements were recorded as in Figure 1.

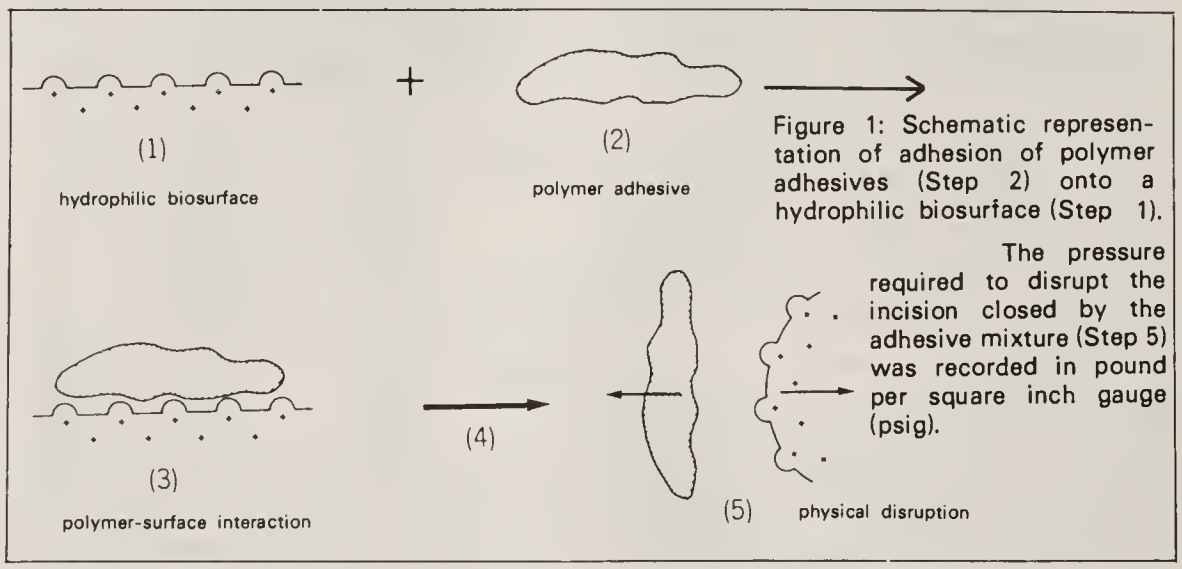


Figure 1: Schematic representation of adhesion of polymer adhesives (Step 2) onto a hydrophilic biosurface (Step 1).

Comments

Inconsistencies in earlier adhesion studies may be attributed to the lack of proper control of experimental variables. Extensions of synthetic polymer adhesions to cell-cell recognition processes poses some fundamental problems, the most significant being the complexity and incomplete understanding of the cell and its surface. Such problems necessitate the limitation and control of identifiable experimental parameters, in the hope of gaining some insight into bioadhesion, whilst relying on as few assumptions as possible. A more suitable way to identify and control these variables appears to be the use of a model system which changes predictably with experimental conditions. Such models involving the interactions between the plant lectin Concanavalin A and murine 3T3 fibroblasts have been suggested[3 8] providing an intermediate step in approaching the cell-cell recognition problem.

Indeed, lectin binding to specific carbohydrate residues support the crucial role cell surface sugars play in agglutination. This poorly understood property of lectins to control highly species-specific aggregation processes has prompted the search for animal lectin cells as a possible key to cell-cell recognition processes[6].

Finally, a similar ligand-induced cell surface phenomenon has been observed with B-lymphocytes. Nature endows these cells with the potential to recognize one specific antigen. When stimulated by antigen, immunocompetent (mature) B-lymphocytes are transformed into antibody-producing plasma cells. The combination of antigen and antibody produces a complex which is eventually phagocytosed with the help of complement or other opsonins.

In conclusion, synthetic non-biological antigen polymers offer yet another opportunity to study polymer-surface interactions on a molecular level. Hopefully, this approach will provide further insight into the complex problem of polymer-surface interactions and bioadhesion. □

Acknowledgements
This work was supported in part by the Medical Research Council Canada, Grant No. MA-5666. M.J.B. is the recipient of a Samuel Castrilli Medical Research Award.

References:

1. Brash, J.L., Lyman, D.J.: *The Chemistry of Biosurfaces*, ed M.L. Hair (New York: Marcel Dekker, 1965)
2. Chatoraj, D.K., Bull, H.B.: *J. Amer. Chem. Soc.*, 81:5128, 1959
3. Evans, D.W., Wang, P.Y.: in "Carbohydrate-Protein Interaction", ed. I. Goldstein. *ACS Symp.* 88:76,1979
4. L. Thomas, E., Wang, P.Y., Cannon, J.S.: *J. Biomed. Mater. Res.*, 8:35,1974
5. L. Thomas, E., Wang, P.Y., Vinals, J.: *Biomat, Med. Dev., Art., Org.*, 1(3): 507, 1973
6. Sharon, N., *Sci. Am.*, 243(5):90, 1980
7. Wang P.Y.: *Nature*, 249:367, 1974
8. Wang, P.Y., Evans, D.W., Bazos, M.J.: *In press.*
9. Wang, P.Y., Forrester, D.H.: *Trans. Amer. Soc. A*[12]:831, 1978
9. Wang, P.Y., Forrester, D.H.: *Trans. Amer. Soc. Artif. Int. Organs*, XX: 504, 1974
10. Wang, P.Y., L. Thomas, E.: *J. Biomed. Mater. Res.*, 12:831, 1978
11. Weiss, L.: *The Chemistry of Biosurfaces'*, ed M. Hair, (New York: Marcel Dekker, 1972).

Validation Studies of a New Model of Myocardial Perfusability

David Malkin 8T4
Colin Bayliss 6T1

The interventricular rabbit septum preparation is a new model of myocardial perfusability. If a large number of precapillary vessels were cut in the dissection of the septum, this would result in a serious underestimate of the pressure component of the pressure-flow relationship which constitutes perfusability. By showing that only 8.2% of infused 50 micron microspheres escaped from transected precapillary vessels, this study demonstrated that the new model is a valid preparation for the investigation of myocardial perfusability.

Introduction

Severe ischemia, in the form of a heart attack, occurs when there is a critical imbalance in the oxygen supply-demand status of cardiac muscle. Less severe ischemia may also result from elective cardiac arrest for cardiac surgery. It is valuable to have a reliable model for investigating the beneficial effects of reperfusing the myocardium in both situations. This paper describes continuing validation studies of such a model[1].

When myocardial perfusion is critically reduced for any reason, an impediment to reperfusion develops. The longer the initial reduction in perfusion, the more serious is the impediment to reflow. It has been previously shown[2] that the major cause of reduced reflow is coronary vascular compression by myocardial contracture, a condition analogous to rigor mortis in skeletal muscle.

Any experimental study of myocardial perfusability requires a model that accurately controls preload, afterload, heart rate and contractility while measuring coronary pressure-flow relationships. A promising new model[1] is the isolated, perfused rabbit interventricular septum preparation (Fig. 1). Fresh blood is recirculated from an awake rabbit through the septum, which is stimulated to contract isometrically against a tension transducer. Coronary perfusability, the relationship between pressure and flow, is derived from the pump speed and the perfusion manifold pressure. The septum is supplied by a discrete vascular bed arising from the septal artery. The septum is representative of the left ventricular myocardium and is used as a model of regional ischemia. To create ischemia, the pump is turned off; to study reperfusion, the pump is turned on again.

A problem arises in the preparation of this model. Excising the septum transects coronary vessels at either the pre-or post-capillary levels. It is important to know which level is affected. If precapillary vessels are cut, leakage of blood decreases the intravascular pressure normally controlled by arterioles and artifactually reduces the calculated resistance (pressure/flow). If post-capillary vessels are cut, no such artifact occurs because these vessels are beyond the major resistance level of the microcirculation.

The purpose of this study was to determine the proportion of precapillary vessels which were transected. A small proportion, less than 10%, would validate the septum model for studies of post-ischemic perfusability.

Methods

Each of 5 septae were studied as follows. Between 1000 and 10,000 50u microspheres, the size of precapillary arterioles, were evenly distributed in a small plastic petri dish. A piece of millimeter graph paper was taped beneath the dish which was observed through a conventional light microscope at 20 x magnifification. All the microspheres were counted twice. Dextran-40 (194.7 mg) was added to 1 ml of Normosol containing a few grains of Pluronic F-68 detergent to produce a suspending solution for the microspheres.

The known quantity of suspended microspheres was drawn into a 5 ml mixing chamber containing a small magnetic stirrer (Fig. 2). The mixing chamber was placed between the pump and the rabbit septum. Heparinized blood was perfused through the mixing chamber for 20 minutes at a flow rate of 1 ml/min, carrying microspheres into the contracting septum. The circuit from mixing chamber to septum was rinsed at the end of the procedure and its content of spheres subtracted from the number originally loaded into the chamber, to determine the number that perfused the septum. The effluent was counted for microspheres.

The septum was flushed with 40% formalin, fixed in 2% formalin, then dehydrated in progressively concentrated ethyl alcohol. It was placed in methyl salicylate for two months to produce optical clearing. The cleared septum was photographed at 20x magnification to determine the randomness of microsphere distribution.

It was important to see if myocardial contracture interfered with the identification of transected vessels by impeding the passage of spheres. For each septum, the amount of contracture at 20 minutes of perfusion was correlated with the number of microspheres in the effluent. Contracture was measured by resting tension expressed as a percentage of its control value at the start of perfusion.

It was also important to determine the correct microsphere perfusion time. If this time was too short, possibly not enough spheres would enter the septum to identify transected vessels, if they existed. If the perfusion time was too long, it would be possible for a large number of spheres to pass through a small number of transected vessels, thus overestimating their proportion. The mixing chamber was loaded as described for septal perfusion and the delivery profile of microspheres was determined over 30 second intervals for 30 minutes. The optimum perfusion time was that interval encompassing peak delivery in two trial runs.

Results

The variation in duplicate counts of up to 10,000 microspheres was less than 10%. The process, though tedious, was aided by the graph paper coordinate system and the mechanical microscope stage.

As vessels became occluded by spheres, perfusion pressures rose and variable levels of contracture occurred. Table 1 shows the results in 5 septae. An average of 8.2% of perfused microspheres escaped through transected precapillary vessels greater than 50u in diameter. Associated levels of contracture ranged from negligible (104.9%) to extreme (347.7%) but did not correlate with the proportion of escaping microspheres (fig. 3).

Figure 4 shows that the majority of spheres loaded into the mixing chamber were delivered to the septum by 20 minutes. This was chosen as the optimum perfusion time.

Figure 5 shows a typical cleared septum. The distribution of microspheres is random and suggests that most precapillary vessels were exposed to the spheres.

Discussion

An important criterion for the usefulness of the septum model is the validity of its estimation of perfusability, the relationship between pressure and flow in the coronary circulation. The flow component can be measured accurately by a calibrated pump. However, the pressure component is subject to underestimation if precapillary vessels are transected in the preparation of the model.

This study suggested that only a small proportion (8.2%) of the precapillary vessels were transected. This is a valid conclusion only if spheres of adequate size and quantity were used, only if all vessels were perfused, and only if the inevitable contracture did not impede microsphere escape through transected vessels.

The use of 50u spheres ensured that only precapillary vessels were sampled. The fact (Table 1) that both the largest (10088) and the smallest (1670) quantity of spheres resulted in equal (0.1%) escape, suggested that microsphere loads within this range were adequate and did not affect the outcome. The 15.4% escape in two septums could have been due to either moderate numbers of open vessels or as few as one open vessel perfused too long. The limit of 20 minutes perfusion and the adequate sphere distribution minimized the latter possibility and showed that, sometimes, large vessels will inevitably be cut. Neither distribution nor transmission appeared to be influenced by contracture, provided the perfusion interval was at least 20 minutes.

This study suggests that the septum model is a reliable preparation for the investigation of myocardial perfusability.□

Acknowledgements

The authors gratefully acknowledge the invaluable contribution of Richard Baffour, B.Sc. This work was supported by grants from the Ontario Heart Foundation and the Department of Surgery, University of Toronto. David Malkin was a summer student in the Institute of Medical Science and an elective student in the Department of Surgery.

References

1. Bayliss CE, Crawford FB and Nsafoah B: The Interventricular Septum — An Isolated Perfused Model for Assessing Myocardial Function. *Canad. J. Physiol. Pharmacol.* 55:1358-1368, 1977.
2. Bayliss CE, Baffour R and Crawford FB: Myocardial Contracture — The Predominant Cause of Impeded Reperfusion in Simulated Surgical Ischemia. *Canada. J. Surg.* 24:260-264, 1981.

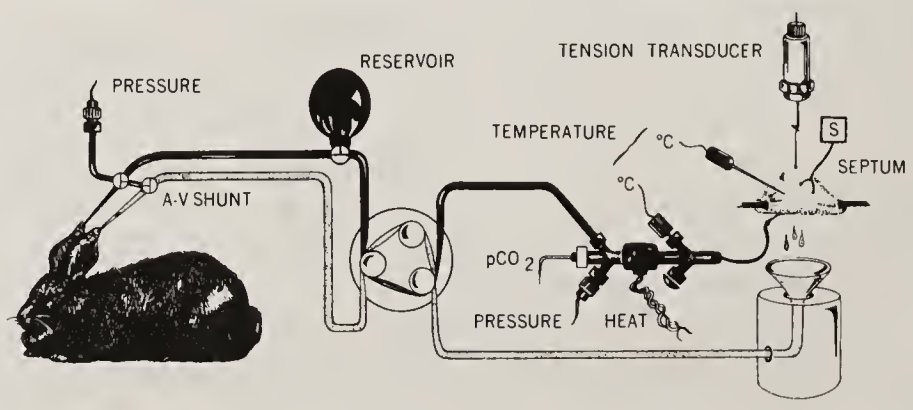


FIG. 1: Septum model. Arterial circuit black; venous circuit stippled. Studied of post-ischemic reperfusion are done with the rabbit out of the circuit and the A-V shunt open.

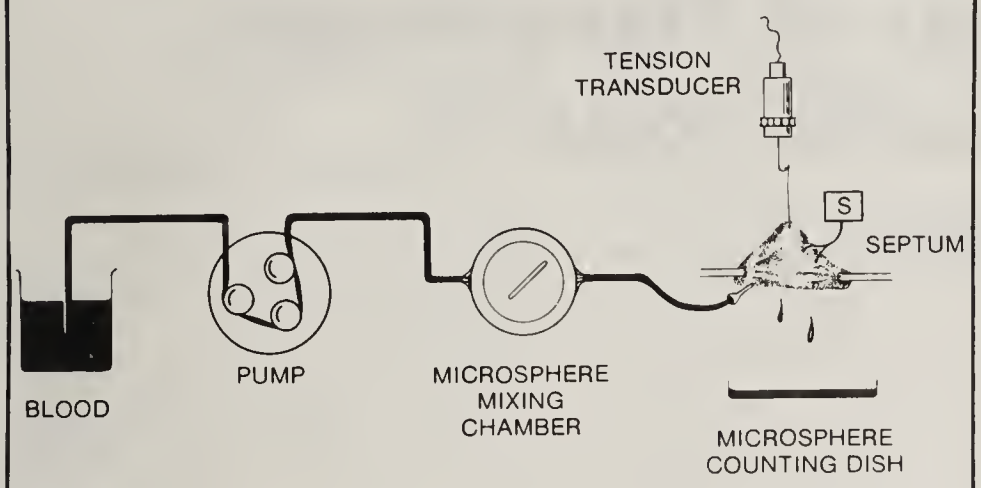


FIG. 2: Microsphere perfusion system.

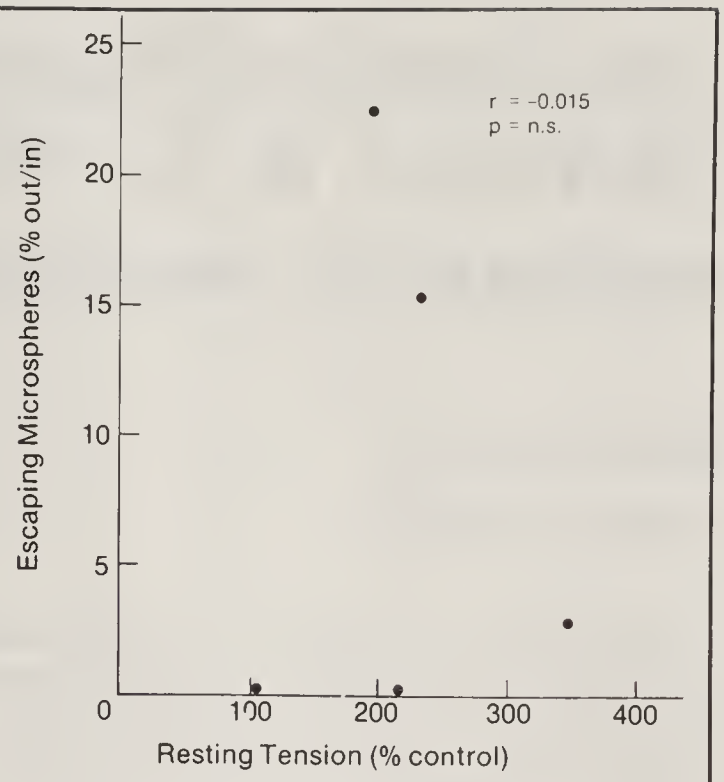


FIG. 3: Lack of correlation between contracture and escaping microspheres. Contracture is resting tension after 20 minutes perfusion, expressed as a percentage of resting tension at the start of perfusion.

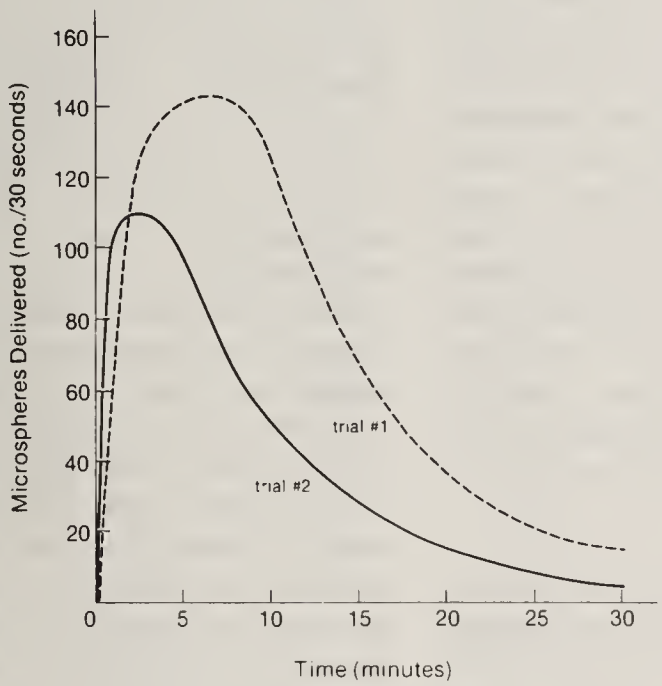


FIG. 4: Microsphere delivery profile showing 20 minutes to be the optimum perfusion interval.

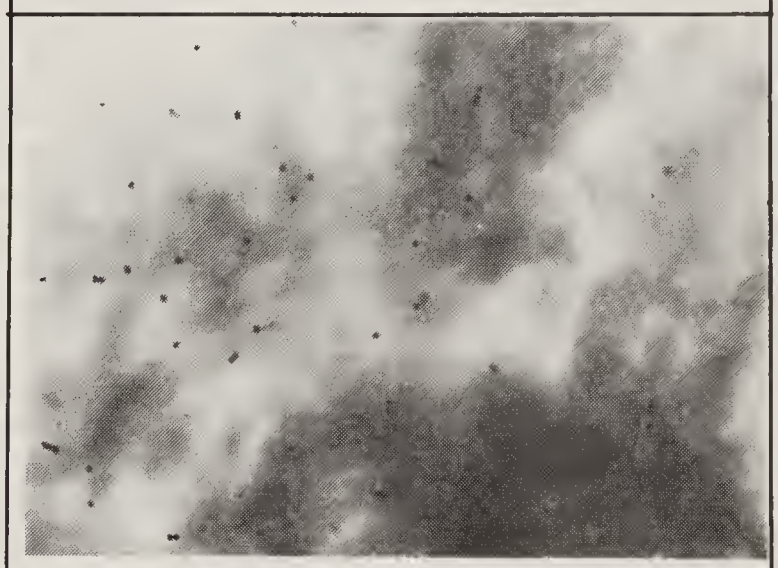


FIG. 5: Typical septum showing random distribution of microspheres. Original magnification x20. Microspheres 50u diameter.

TABLE 1
50u MICROSPHERES

Septum	In *	Out *	Out/ In (%)	Contracture ** (% control)
1	1670	2	0.1	104.9
2	3142	85	2.7	347.7
3	10088	11	0.1	217.3
4	4156	640	15.4	232.6
5	4026	906	22.5	192.3
			Mean 8.2	

Table 1: Proportion of perfused microspheres escaping through transected precapillary vessels. Associated septal contracture.
*Duplicate count of absolute numbers.
**Resting tension after 20 minutes perfusion, expressed as a percentage of resting tension at the start of perfusion.

Biochemical Aspects of Plasminogen Activator & its Possible Role in metastatic neoplasms

Raymond Ng*
Andie Lam 8T4

Plasminogen Activator (PA) is a serine protease capable of activating the proenzyme Plasminogen to its active form Plasmin. The level of PA has been shown to increase significantly in transformed cells as well as in many types of human carcinomas and some sarcoma lines. Furthermore, experiments using animal models to study the mechanism of metastasis seem to indicate a correlation (both positive and negative) between tumor PA levels in-vitro *and the tumors' metastatic potential* in-vivo. *These observations, collectively, not only suggest that PA may be useful as a tumor marker, but it may also play a crucial role in the process of metastasis. This paper starts with an introduction covering the physiological + biochemical aspects of human PA, and then presents some of the reported observations on tumor PAs. The latter part of this article will be devoted to the discussion of how PA may participate in the process of metastasis. While some of the proposed mechanisms remain hypothetical, experimental conclusions which either support or defeat the hypothetical role of PA will be delineated.*

INTRODUCTION

One of the most significant and perhaps lethal features of malignancy is the ability of the tumor cell to invade and implant at distant sites in the body resulting in formation of secondary tumor foci a process known as metastasis most benign, localized tumors can be resected surgically or treated with irradiation, widespread dissemination of malignant tumors renders surgical therapy very difficult for the patient although medical treatment may help. Frequently, growth of tumors progresses insidiously without any noticeable clinical manifestations; hence, by the time the disease has become symptomatic, metastasis has already occurred. Therefore even the most comprehensive surgical procedure cannot significantly improve these patients' prognosis. Combined chemotherapy has also been widely used in many forms of malignancies, but it is well known that secondary tumors often behave differently than the primary and hence, respond to the treatment to a different extent, or even resist it. Malignancy, therefore, is sometimes considered to be a "multiple" or systemic disease rather than a single entity.

In view of the poor prognosis associated with metastasized tumors, specific tumor markers are urgently sought to allow early detection of the presence of the primary, tumors before dissemination occurs. In addition, markers can be utilized to assess the extent of metastasis and to monitor the efficacy of a particular treatment. Unfortunately, most markers presently available cannot satisfy all the criteria of an "ideal" tumor marker[22], which include 1) high sensitivity, 2) tumor specificity, 3) good correlation with tumor burden 4) accurate prognostication 5) Prediction of recurrence 6) Guidance for treatment. Even one of the most commonly used markers, CEA (carcinoembryonic antigen), which provides some correlation with prognostic outcome of the disease, is still not sufficiently specific and sensitive for diagnosing occult malignancies.

Realizing the present, rather limited armamentarium for the diagnosis and treatment of malignancy, one begins to appreciate the intense experimental studies conducted throughout the world in search of better tumor markers. Many "potential" markers are currently under investigation. Most are either tumor cell surface components, or tumor cell secretory products. For instance, it has been known for sometime that human tumors or transformed animal fibroblasts in culture release high level of proteases as compared with their normal counterparts. Hopefully, some of these proteases may soon prove to be useful markers for early tumor identification among the tumor proteases reported, plasminogen activator (PA) recently has been given a great deal of attention, because its activity is elevated in many types of carcinoma, as well as sarcoma cell lines. Its role (s) in the mechanism of metastasis have been very suggestive. Therefore, an attempt will be made in this paper to discuss some of the biochemical aspects of this proteolytic enzyme,

* *Recipient of MRC studentship, presently a graduate student at the department of clinical Biochemistry, Sunnybrook Medical Centre.*

to summarize some of the experimental findings concerning tumor PA, and at last, to delineate some of the possible roles PA may play in the process of metastasis.

Physiology of Plasminogen Activator

Plasminogen Activator belongs to a class of serine proteases which is active at neutral pH and do not require a cofactor for catalytic activity[32]. If converts the zymogen plasminogen (single chain, mw 83,000 to 90,000) to its active form, plasmin (a double chain linked by a single disulfide bond, mw 60,000 and 20,000) by proteolytic cleavage at a limited number of sites[29]. Plasmin is an enzyme with trypsin-like activity. It has a broad specificity but probably the major biological substrate for plasmin is fibrin, the basic constituent of blood clots.

On the basis of molecular weights, PA can be categorized into three classes[17]: 1) urokinase with molecular weight of 55,000 and 30,000, 2) tissue and vascular PAs of molecular weight 64,000 to 80,000 and 3) circulating PAs with molecular weight of 90,000 or greater. Urokinase is probably the most extensively characterized form of human PA, owing to the fact that it is present in relatively large concentrations in the urine. Urokinase has been isolated in highly purified form, and a monospecific anti-urokinase is now commercially available. This latter material allows a variety of immunologial studies of the enzyme, as well as a mean of identifying other types of PA which may be similar to urokinase. Two major forms of urokinase (Mwt 55,000 and 30,000) have been demonstrated[16]. The precise origin of urokinase in the urine is unknown but the renal tubular epithelium and the epithelium of the lower urinary tract are the most likely sources.

The fibrinolytic activity observed in tissues is mainly caused by the tissue type PA. The distribution and content of PA show great species individual and organ differences, but in general, structures such as the uterus, the adrenal, lymph nodes, prostate, thyroid, lung and ovaries have high or medium range of activity. The concentration of tissue PA can be affected by exogenous stimulation or by certain physiological conditions. For example, high levels of PA can be shown in injured tissues undergoing repair[13]. In the case of the vaginal epithelium and the endometrium, the activity is under the constant influence of sex hormones[2]. Activators secreted from stimulated macrophages, polymorphonuclear leucocytes and monocytes are also classified as tissue PAs, and these enzymes are thought to be involved in parenchymal repair during the inflammatory process. While the majority of tissue PAs appear to be identical to or at least similar to urokinase, the activity of some tissue PAs *invitro* may not be affected by the presence of antiurokinase at all, suggesting that *invivo* PAs may in fact be different.

PA of vascular type is most likely synthesized by the endothelium of veins and venules. PA from the arterial endothelium is probably in an inactive form and requires stimulation to be potent[17]. Augmented liberation of vascular PA may account for the observed increase in fibrinolytic activity in blood after venous occlusion; [36] the latter process can lead to blood stagnation and possible local thrombosis. Therefore, it is generally acknowledged that this enzyme is responsible for maintaining the patency of vessels via the lysis of blood clots through its thrombolytic potential along the vascular wall.

The third type, circulating PA, is termed very appropriately because this enzyme is indeed found in the circulation. It is probably generated from precursors in blood which are part of the coagulation system. These include kallikrein, Hageman Factor XI and its fragments, and cofactor. Formation of the blood activator can also be induced by streptokinase, a compound produced by certain strains of hemolytic streptococci and sometimes employed as a thrombolytic agent[3]

Tumor Plasminogen Activator

Several lines of human tumors as well as *in-vitro* transformed animal fibroblasts have been shown to discharge high levels of PA. Although its exact role in tumor physiology and survival is rather obscure, it has been proposed that there is a close link between its level *in-vivo* and the extent of malignancy.

PA in tumors was first demonstrated in 1925 by Fischer who reported that two factors (serum and cellular) were involved in the high fibrinolytic activity in fibroblast cultures from several species, following malignant transformation by oncogenic viruses or by chemical agents. The serum factor was later discovered to be plasminogen, and the cellular factor - PA released by transformed cells. The magnitude of this enzyme increase, ranged from 3 to more than 100 fold, exceeding by far the reported increase of other biochemical changes associated with malignant transformation.[28] For the past several years, high levels of PA have been shown in a wide variety of human tumors such as cervical, mammary, prostatic, ovarian, bladder, lung, kidney, stomach carcinoma, melanoma and basalioma. The increase varies from 3 to as high as 60 folds[24]. Results reported so far seem to support the conclusion that some tumors tend to secrete more than one type of PA.

As mentioned earlier, PAs with distinct physiochemical and immunological properties can be extracted from different tissues or even from the same tissue under different circumstances. More interestingly, however, is the fact that some tumors produce PAs with different immunological characteristics than those in the tissues from which the neoplasms arose!Are these multiple forms of PAs products of different genes or do they arise by differences in processing of a larger precursor molecule? The fact that three or

more different molecular weight species of PA can be produced by an apparently uniform population of cells in culture seems to support a cascade type of processing.[1 34]. On the other hand, a precursor-product relationship is challenged by the observation that the larger form of PA does not corss-react with the antibodies against the smaller form of PAof the same species in the case of SV-40 transformed hamster cells[17]. Separate PA genes seem to be the most plausible explanation so far. This is supported by the finding that tumor promoter TPA (12-0-Tetradecany)-phorbal-13-acetate) can induce production of one antigenic form of PA easily in those tumor cells that actively produce it but do not stimulate PA production in tumors that manufacture a different form of PA[12]. This is consistent with the separate gene model in which TPA may activate one set of PA genes but not in other. Lack of TPA receptors in "non-responsive" cells has been ruled out since these cells do in fact show some changes in morphology in the presence of TPA. Therefore, in human systems, there are probably several distinct genes coding for different species of PA, and perhaps, two or more genes may give rise to higher molecular precursors which are subsequently processed to lower molecular weight species.

Since the exact function of PA in normal tissues and tumors is not fully understood, most of the discussion below remains hypothetical although some experimental evidence is presented. It has been shown both *in-vitro* and *in-vivo* that many tumor characteristics are intimately associated with PA activity. It is known that a number of *in-vitro* cell characteristics (both normal and malignant) including morphology[25], growth rate, saturation desnity[8 9], motility[25] and agglutinability[14] can be altered by addition of exogenous proteases or protease inhibitors. For instance, anti-fibrinolytic agents can reduce cell motility and delay expression of certain malignant characteristics, and some tumor cells in culture even require plasminogen for manifestation of malignancy. Cells transformed by DNA or RNA oncogenic viruses are agglutininated more by some plant lectins than their comparable normal cells. This change in agglutinability is the result of an altered cell surface due to the action of plasmin. On the other hand, a major surface glycoprotein (fibronectin) of most normal fibroblasts and endothelial cells called LETS (Large External Transformation Sensitive) has been found to be highly sensitive to proteolytic attack[16] and is absent or greatly reduced in most transformed cells.[31] This change in surface glycoprotein content is suggested to be the factor leading to changes in morphology. growth saturation and other tumor associated *in-vitro* characteristics. Addition of the matrix form of fibronectin, solubilized by urea and alkali, to transformed cells restores normal morphology and increased adhesion to the substratum[39]. Similarly, human sarcoma cells assume the appearance of normal fibroblasts when seeded on cell-fee pericellular matrix isolated from fibroblast cultures[39]. Cellular attachment and migration of tumor cells *in-vitro* are probably a complex process requiring several tumor factors, but PA activity, with the active plasmin as the general protease, has been shown to be one of the participating systems affecting the degree of attachment and rate of migration[35].

The role of PA in Metastasis

Dissemination of tumor cells can spread via a combination of 1) blood stream, 2) lymphatics, and 3) serous cavities. Nevertheless, the essential first step for metastasis is the phenomenon of tumor invasion. Cancer cells must first detach from the primary site and penetrate the surrounding normal cell matrix. In the case of blood-borne metastasis, the neoplasm must perforate the surrounding vasculature for entry and dissemination, a process named intravasation. Similarly, extravasation and the ensuing implantation may be envisioned as the reverse operation.

Invasion is probably a multiple-step process necessitating the participation of many tumor factors with precise coordination of each type of activity at the proper time. Since any single tumor mass consists of a heterogenous population of tumor cells in various stages of differentiations, only those highly invasive cells with the proper programmed sequence of actions and a sufficient defence mechanism against the host response can them successfully give rise to secondary foci. Few tumor cells will have all these characteristics; therefore metastasis may be considered as an "inefficient process."

Three general mechanisms have been proposed to explain tumor cell invasion: 1) rapid proliferation of malignant cells, resulting in infiltration and growth by mechanical pressure, 2) decreased tumor cell cohesiveness associated with increased cellular motility, and 3) destruction of host stroma by the secretion of lytic enzymes. These mechanisms may not be mutually exclusive and each may play a more important role dependent on the type of neoplasm. Recently, with the discovery of high proteolytic activity associated with certain tumor cells *in-vitro*, greater attention has been given to the third mechanism. Many types of proteases have been shown to be secreted from the malignant cells, each of which may contribute to a different extent to the overall process of metastasis. However, with the enormous supply of plasminogen in tissues and the broad specificity of plasmin, PA may in fact play a very significant role in tumor invasion.

For tumor invasion to begin, a subpopulation of highly invasive cells from a neoplasm must first disengage from the primary site. A possible mechanism for the cell detachment may be "sublethal

autolysis" by lysosomal enzymes[27] or simply by cell surface associated enzymes. Adhesiveness of normal cells appears to depend on proper alignment of the sugar end of the surface glycoprotein in one cell with the tightly binding surface glycosyltransferase of another cell. PA released by the tumor cells or membrane-bound PA can generate plasmin, which digests these surface components and leads to displacement of one or more binding substances. The lack of proper arrangement of these constituents reduces the degree of cellular anchorage and adhesiveness. Furthermore, these surface glycoproteins are secured to the underlying cytoskeleton, which probably serves to maintain a normal cell shape and which may regulate cell motility *in-vivo*. Breakdown of these glycoproteins results in disruption of the intracellular organization of the cytoskeleton; hence, the tumor cells may now assume many different shapes with greater motility.

The loss of surface fibronectin also leads to the disappearance of the so called "contact inhibition", a phenomenon in which normal cells stop dividing after contacting each other. The lack of "contact inhibition" obviously further facilitates invasion by allowing continued rapid proliferation of tumor cells which increases mechanical pressure therefore, a decrease in glycoproteins has been reported to be associated with an increased metastatic potential.

Following detachment from the primary site, tumor cells must next traverse the barriers of normal extracellular matrix before they reach the vessels. The extracellular environment of solid tissues is well organized; it is composed mainly of large molecules, namely collagen and proteoglycan. These molecules contribute to the strength and elasticity of tissues and are susceptible to proteolysis[4]. For example, proteoglycan is highly sensitive to cleavage by plasmin although collagen is not.

However, collagen can be digested by plasmin indirectly. Like most proteases, collagenase is produced in both a latent and an active form[15]. The plasmin formed from plasminogen can actually convert the latent collagenase to an active form which digests collagen. Thus, the enhanced production of PA may lead to a higher level of both the general proteinase, plasmin, and the specific proteinase, collagenase. It must be emphasized, however, that other tumor cell proteases are capable of converting latent collagenase to its active form as well. Plasmin generated by tumor PA not only can destroy the adjacent extracellular matrix, it may also result in normal cell injury and necrosis. Infarction may secondarily be due to a diminished blood supply caused by the obstruction of local capillaries or small vessels by the rapidly expanding tumor mass. Following necrosis, infiltration by macrophages and leucocytes occurs (a normal response to cell death). This promptly triggers the release tissue PA into the damaged area. Thus tissue PA may actually "open up" a path for the invading tumor and further facilitate metastasis.

During the hematogenous metastatic process, tumor emboli must traverse the continous vascular endothelial basement membrane (BM). In fact, local dissociation of the BM by tumor cells can be demonstrated by electronic microscopy. BM consists of various collagens such as type 4 and 5 collagen, and noncollagen constituents such as laminin and fibronectin. Many of these components appear to be susceptible to plasmin attack with the exception of type 4 collagen, which is a major structural protein present in all BM. However, this type of collagen is more extensively glycosylated as compared with other types of collagen; and it has been suggested that plasmin may remove the sugar moiety of the protein, exposing the collagen core structure to be attacked more readily by other enzymes such as collagenase. In short, it is possible that plasmin alone is not sufficient to completely degrade the entire thickness of BM but it may play a very crucial role in the destruction of the noncollagenous element of the BM, as well as to enhance digestion of collagenous components by other enzymes[21].

As can be understood from the earlier discussion, plasmin formed from the tumor PA may play a key role in the process of tumor invasion. More direct evidence linking the tumor PA with metastasis comes from the experimental results in animal models. In particular, it has been found that induction of fibrinolysis by prolonged treatment with heparin increased metastasis in mice which had been previously innoculated with sarcoma cells[19]. A similar increase in metastasis by heparin treatment is observed in mice transplanted with rhabdomyosarcoma cells cells transformed by chemicals[6]. Enhance hepatic and pulmonary metastasis in mice can also be achieved by pre-treatment with Arvin, an agent which depletes circulating fibrinogen. Furthermore, fibrinolysis induced by human plasminogen in mice increases the incidence of metastasis, whereas anti-fibrinolytic agents such as Tranexamic acid decrease metastasis[26]. Malignant tumor cells with greater ability to stimulate fibrinolysis *in-vitro* more frequently induce tumors in immunosuppressed animals *in-vivo*[20].

In short, it is theorized that tumors with high fibrinolytic activities should be able to digest the surrounding fibrin and penetrate into the circulation much more easily than do tumors containing less fibrinolytic activities indeed, more recent experiments with B16 mouse melanoma cell sublines further lend support to this hypothesis. It was found that those tumor cells sublines with low PA production had a metastatic incidence of 9.1%, whereas those sublines with significantly higher PA production than the FG had a metastatic incidence as high 75%. Thus suggests that the quantitative

differences of PA exist between the two sublines may contribute to the observed difference in their metastatic potential[37].

Despite all the logic of this working hypothessis, contradictory results have been reported. Histologically fibrin depositions which believed to be the consequence of neoplastic thromboplastic activity may sometimes be seen round the tumor cells. However, this may have several implications for tumor survival. Firstly, fibrin matrix around the tumors may serve as a track or pathway for the proliferation and vascularization of tumor cells to occur. Secondly, fibrins may shield the tumor cells from the host deference apparatus. Thirdly, even more important, is the fact that fibrin deposition around the tumors may permit further aggregation of blood coagulation components such as platelets in the case of blood-borne metastasis. Fibrin formation and hence platelet aggregation are important to the ultimate formation of metastasis, since these processes allow the formation of tumor-microemboli of sufficient size in the vessel which then, in turn, lead to the lodgement of tumor emboli within the capillaries at sites distal from the primary tumor site, a fundamental process before extravasation can even occur. Platelet aggregation is believed to increase vascular permeability at the site of thrombosis, expediting the occurrence of extravasation.

Only under the above considerations can tumors with high fibrinolytic activity be expected to show *reduced* incidence of metastasis rather than the opposite as discussed earlier. Dissolution of fibrin around the tumor mass would prevent tumor proliferation and vascularization and enhance cell death by permitting the penetration of host killer cells. Furthermore, digestion of fibrin by tumor PA generated plasmin impairs the formation of tumor emboli and platelet aggregation and therefore prevents lodgement and extravasation to occur. At present, direct evidence for this mechanism may be lacking, but some indirect evidence do exist. For example, it has been shown in some experiments that factors which influence thrombus formation and therefore tumor cell lodgement do have a great impact on the subsequent formation of metastasis. Agents which can promote thrombus formation tend to promote tumor cell lodgement, leading to increased incidence of metastasis, whereas agents capable of inhibiting coagulation tend to reduce this incidence. For instance, the anticoagulant warfarin effectively reduces the number of lung metastasis in mice when tumors are implanted in the thigh or injected intravenously[7]. Furthermore, tumors with low thromboplastic activities are found to have fewer metastatic foci in lungs of rats than those with high thromboplastic activities. Finally even better evidence for this argument comes from the experiment in which administration of urokinase decreases the number of metastatic foci in the lung of rabbits injected intravenously with V2 carcinoma[18]. It is assumed that plasmin formed from the plasminogen by the action of urokinase removes the fibrin deposit around the embolized tumor cells and restrains lodgment and/or extravasation. It must be emphasized here once again that fibrin formed around tumors may also serve as a barrier against tumor expansion and entry into blood-stream or lymphatic system; thus, removal of fibrin by tumor induced fibrinolysis may actually promote tumor growth and enhance metastasis.

Confronted with such complex and confusing phenomena, one must admit that the real consequences of tumor induced fibrinolysis and fibrin deposition are not resolved. Apparently, in order to gain further insight in this field of study, several variables must be considered and well controlled simultaneously (although this may be exceedingly difficult to achieve). These include the *in-vitro* experimental conditions, the immunogenicity of cancer cells, the potency of host defence mechanism, the enzymatic capacities of cancer and host cells and the characteristics of blood flow through the tumors.

Conclusions

Some plasminogen activators might be potentially useful as markers for a variety of cancers due to the fact that their levels are elevated in a wide array of carcinomas as well as some sarcomas. However, its clinical application is still remote and a great deal of effort is needed to validate PA as tumor marker. This enzyme complex is not easy to measure in the circulation partly because of the presence of enormous amounts of fibrinolytic inhibitors. Complication also stems from the fact that PA can be released from a variety of normal tissues, particularly the vascular system, and hence masking the tumor PA.

Whether PA does contritube to the overall process of metastasis is of more than academic interests. While it is true that conflicting results have been reported, it is fortunate in one sense that tumor cell variants with high PA and low PA production have been successfully cloned and their differences in metastatic potential are now being intensively investigated, and perhaps, not very far from now, a new frontier in our knowledge of the mechanism of metastasis can be established. □

Acknowledgements

Mr. Ng would like to thank Dr. A. Malkin for his advice and guidance. The authors are also indebted to Dr. D.J. Sutherland and to Dr. J.A. Kellen for their support and editorial assistance.

(Reference upon request)

Gastrointestinal Endoscopy: The Past and Future

Paul Boughen 8T3

From man's earliest days, there has undoubtedly been a curiosity about the interior of the body — those "dark places" of the human organism. We all pause periodically to muse about "how we tick" and the popularity of television documentaries showing pictures of the insides of living bodies or organs, especially the gravid womb and the circulatory system, parallels the interest of the medical profession in exploring interior structures. Certainly the majority of medical ingenuity has been directed toward attempts to "see" the innards of the sick individual. Witness the ubiquitous use of the magic ray of Roentgen and the development of ultrasonic techniques. Surgery provides the definitive technique for direct examination of the living body cavities and it is not at all rare for exploratory surgery to play a prominent role in diagnosis today.

However, there is another very useful technique which has been devised to enable doctors to examine the interior of various organs. It is the field of endoscopy, and the story of its development is told here primarily as it relates to the gastrointestinal tract.

For anyone who has ever seen the sword-swallowing act at a side show, it may come as no surprise that long, straight pieces of metal can be introduced in the upper gastrointestinal tract without harm to the individual. Kussmaul back in 1868 saw a similar show. He was interested in looking into the human stomach and he postulated that it must be possible to align the teeth, esophagus, and stomach. (fig. 1) So he hired a sword-swallower and convinced him to "swallow" a hollow metal tube, and holding a lamp close to the proximal end, he looked down the tube. He didn't see anything — it was too dark.

FIG. 1

"Sword swallowing" gastroscopy with a rigid gastroscope.

But Kussmaul can't be credited with the first endoscopy experiment. Bossini, as early as 1795, was using a candle-powered contraption to look into the uterus and rectum.

Bozzini's examinations were likely very quick and mercifully so, with an open flame so close to delicate tissues. Any discomfort

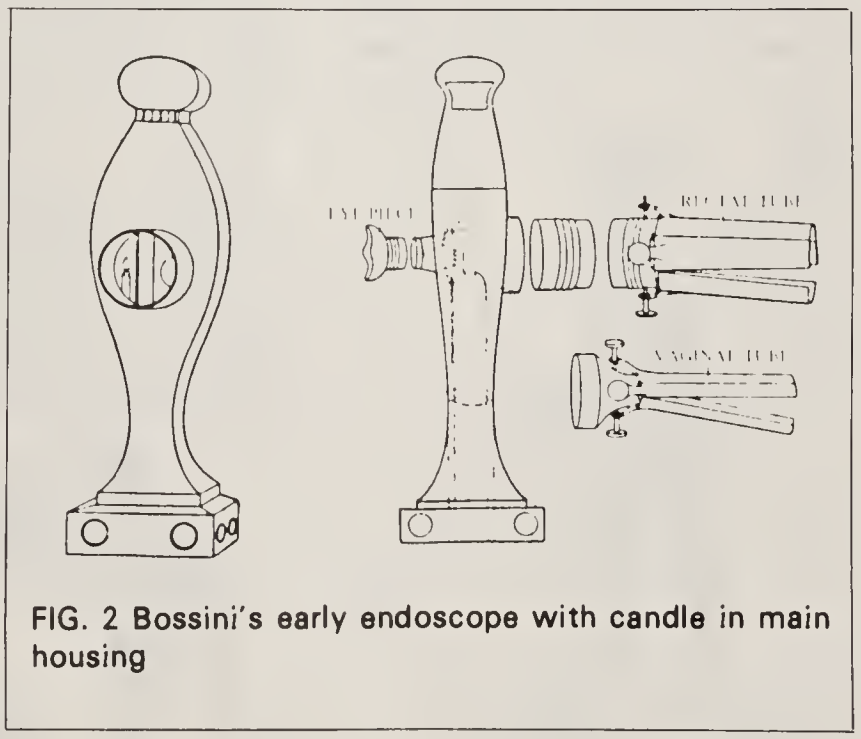


FIG. 2 Bossini's early endoscope with candle in main housing

due to heat was obviously largely ignored because not much later (Desmoreux, 1853) an alcohol-turpentine lamp (fig. 3) was employed to shed even more light (and heat!) on the area.

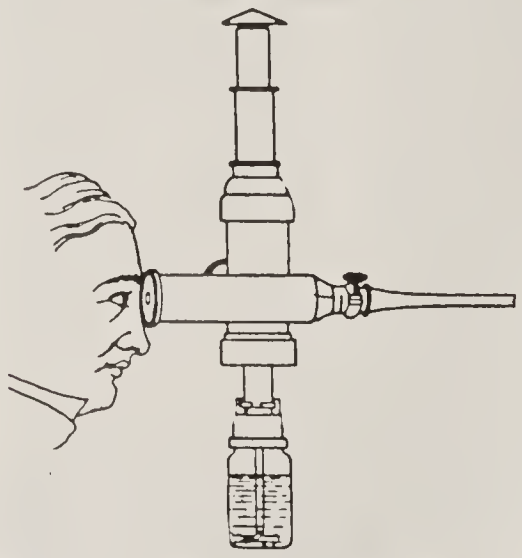


FIG. 3 The turpentine-alcohol flame endoscope required a chimney above the viewing tube.

The next cavity to receive attention was likely the bladder. The early cystoscopic instruments, especially the version pictured here (Nitxe-Leiter, 1879) were however doomed to failure not least because of their gargantuan dimensions. (fig. 4)

Investigations of the upper gastrointestinal tract attracted little attention until the uncertainty about the safety of placing filament containing lamps inside the body has waned. The first use of an electric lamp at the distal end of an endoscope took place in 1906 (Rosenheim). Previously the light had been reflected down the instrument from the eye-piece and never provided enough illumination to permit adequate visualization of anything beyond the proximal esophagus.

FIG. 4 An early uroscopist carrying his instrument.

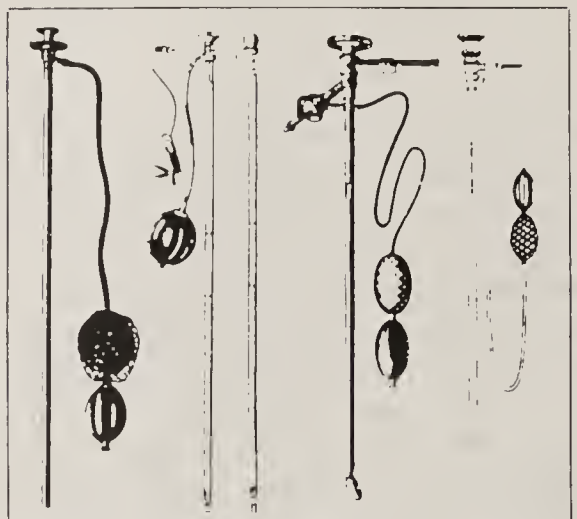


FIG. 5 A collection of rigid gastroscopes.

The gastroscopes in the early days were all rigid devices even as late as 1932. (fig. 5) Many models and alterations were tested, some with permanent bends in them, others that would straighten out after insertion. They all contained lenses and mirrors and some investigators developed bizarre examining postures for their patients to attempt to overcome the difficulties of introducing the rigid endoscope into the stomach, and to permit as complete an examination as possible. (fig. 6)

The name of Rudolf Schindler is intimately associated with the development of modern gastroscopy. In 1923, he published his landmark treatise "Lehrbuch und Atlas der Gastroskopie". Based on hundreds of examinations done with rigid gastroscopes, Schindler's monograph illustrates both normal and diseased stomach and gives birth to the era of endoscopic study of gastric pathology.

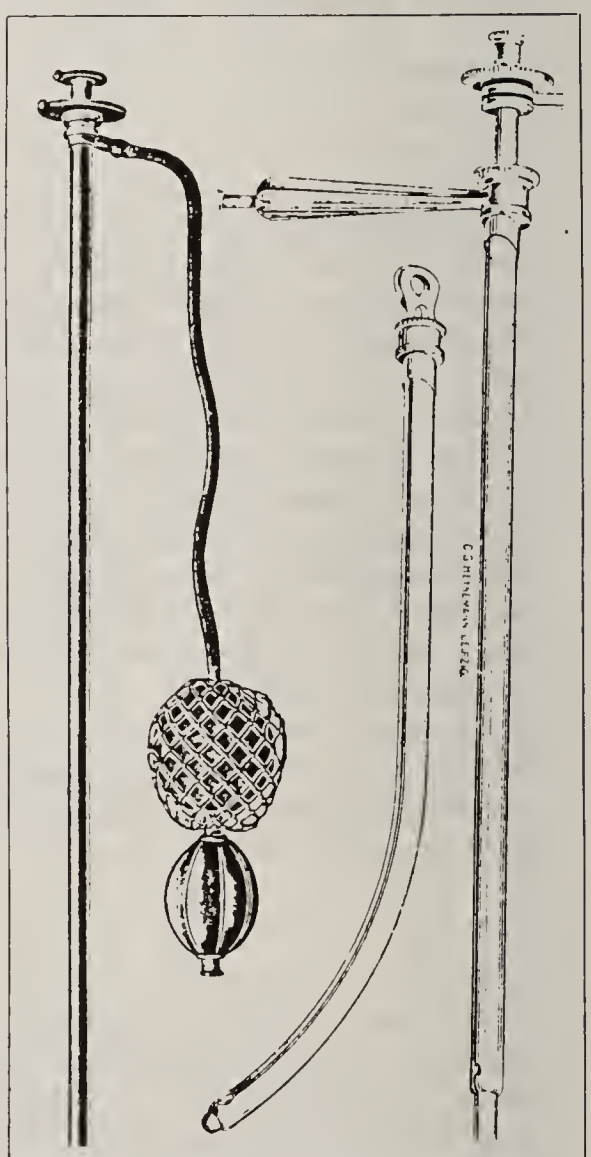


FIG. 7. Three rigid gastroscopes used by Schindler, one with an inflating bulb.

FIG. 6 Sequence of positions for gastroscopic examination.

In 1932, based on an optical principle discovered in 1917, the short but productive period of semi-flexible gastroscopy began. Land found that light could be refracted around a gentle curve using a series of lenses. With a light source at the distal end of the gastroscope (within the stomach) these instruments employed up to 50 thick, short focal length lenses contained within a flexible tube to carry the image to the viewing end of the instrument. (fig. 8) The images produced were remarkably good provided the degree of curvature remained small. One particular instrument was 124.5 cm in length and only 12mm in width over the flexible section, considerably narrower than the modern fibre-optic gastroscopes.

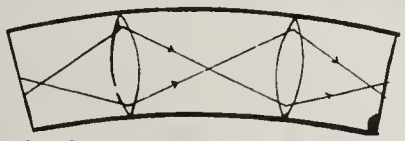


FIG. 8. Optics employed in semi-flexible endoscopes showing lenses.

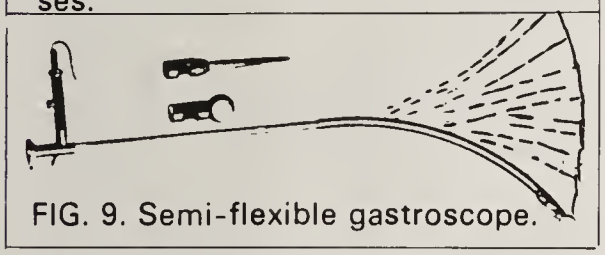


FIG. 9. Semi-flexible gastroscope.

The semi-flexible gastroscopes in fact could only be bent over the distal rubber-covered segment, the upper portion being a rigid metal tube — hence the name. But this flexibility greatly increased the ease with which the gastroscope could be introduced. Pull wires were added to later instruments to permit movement of the flexible portion in one dimension. (fig. 9) Other modifications followed, the most important of which was the "omniangle" gastroscope employing an adjustable mirror at the distal end of the gastroscope. These improvements afforded the viewer an ever increasing panorama of gastrointestinal mucosa. However, four "blind spots" remained (fig. 10) and technical complications, such as esophageal perforation, prevented the widespread use of gastroscopy. Biopsy and photography techniques with these instruments, although attempted, were not terribly successful and did not gain generalized acceptance.

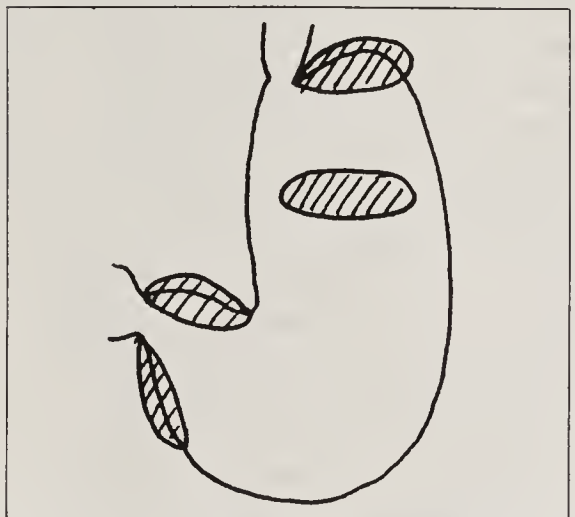


FIG. 10 Blind spots in semiflexible gastroscope.

Nevertheless, Schindler who had moved to U.S.A. in 1934, trained many men from around the world who in turn taught the technique to others.

The discovery of the optical principles that gave birth to the modern era of fibre-optic endoscopy pre-date the first appearance of a workable instrument by over 100 years. John Tyndall, in 1854, first described the phenomenon now called "total internal reflection". It was observed in a liquid stream wherein the light "...seemed to be washed downwards by the descending liquid..." Not until 1927 however, were patents applied for the transmission of images in fibres of silica.

The principle of total internal reflection involves the refraction of a light ray at the interface between two different materials. If the angle between the direction of incident light rays and the interface is small enough the light rays will be reflected (as from a mirror surface) and will remain within the initial medium (fig. 11). This phenomenon has been employed in many branches of science and industry.

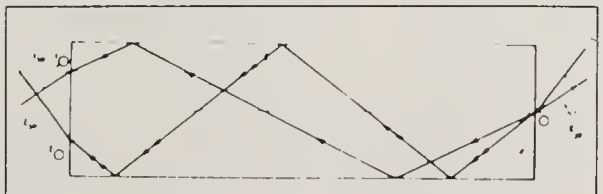


FIG. 11. Total internal reflection as used in fibre-optics.

Modern endoscopes employ monofilaments of coated glass which are grouped in bundles, lubricated and fixed to each other only at their ends. Thus the individual fibres move freely throughout most of their length providing great flexibility. (fig. 12)

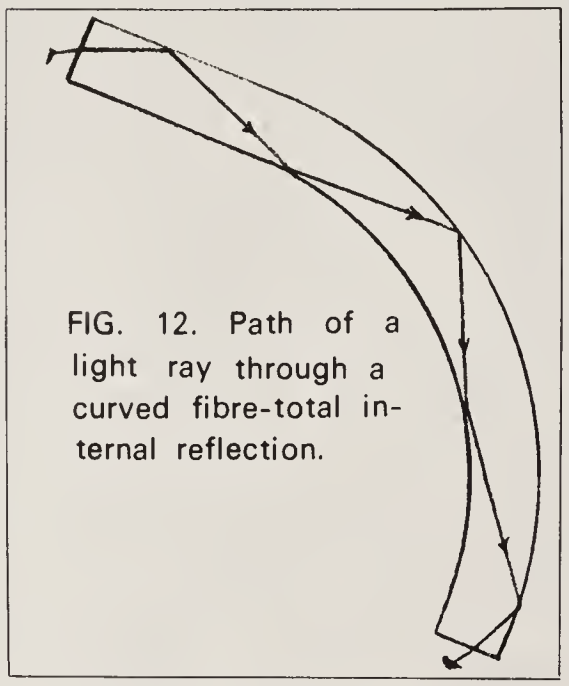
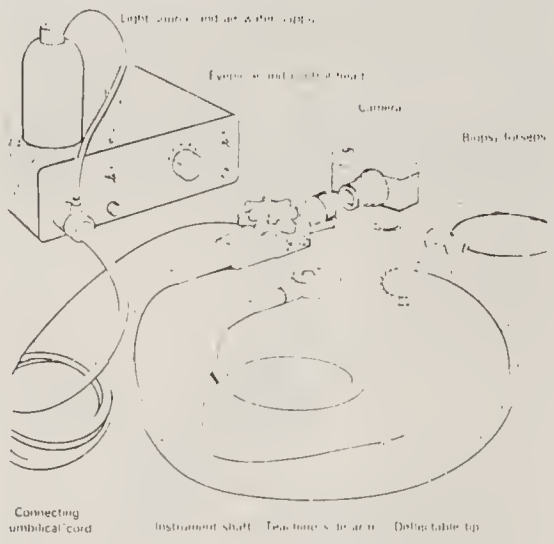


FIG. 12. Path of a light ray through a curved fibre-total internal reflection.

The fibre-optic 'scopes today have many other features which provide excellent imaging and make the instruments safe to use. These include: (a) a "removed" light source which trasmits light to the examining (distal) end of the scope through a separate fiber bundle, thereby eliminating the dangers of having a light source in the gastrointestinal tract itself; (b) ports and channels in the 'scopes allowing flushing, air inflation techniques, biopsy and many therapeutic and diagnostic modes including polypectomy, coagulation, and cannulation of ducts: (c) teaching is made easy with the use of the "teaching head" which is a separate fibre-optic attachment that splits the image between the operator and the observer. Many manufacturers offer camera accessories which provide excellent photographs. An extremely useful addition to the endoscopy technique is the development of video equipment — a video camera is attached to the endoscope and the image is displayed on a television monitor. Excellent for teaching purposes, this accessory also permits the recording of the procedure on magnetic tape.

FIG. 13 Modern endoscope with usual accessories.



It was with the development of fibre-optics that gastrointestinal endoscopy began to show its true value and grow toward its full potential. The first instrument employing the fibre-optics system was used in 1958. It has been due to the refinement of production techniques and engineering and the result of modern manufacturing expertise that have over the past 24 years created the instruments now in use all over the world. What existed only on the drawing-board a quarter of a century ago, is today an essential piece of equipment in both the medical and surgical armamentaria.

THERAPEUTIC ENDOSCOPY

Today, the use of endoscopes to diagnose gastrointestinal pathology is well known to the medical community. Although once described as "an expensive piece of illuminated spaghetti", the endoscope is now an essential piece of investigative equipment. Presently available instruments provide excellent visualization of the entire gastrointestinal tract and special radiological procedures to visualize some accessory glands — namel the pancreas and biliary tree — use endoscopic technique to cannulate the ducts of these organs. In the diagnosis of some emergency conditions, expecially acute upper gastrointestinal hemorrhage, endoscopy is one of the first diagnostic steps.

As medical progress marches relentlessly forward, the widespread use of fibreoptic endoscopes has generated interest in the therapeutic possibilities of the instruments. Much ingenuity has been demonstrated in the refinement of techniques specially suited to the "non-invasive" nature of gastrointestinal endoscopy. It is this characteristic — that intraluminal procedures can be performed while the patient is only moderately sedated — that creates fertile soil for the growth of new ideas and techniques in the management of gastrointestinal disease by endoscopic means.

Several of the most useful and interesting therapeutic uses of gastrointestinal endoscopy are briefly discussed. Some of these procedures are routinely performed today while others are still evolving and have not yet received widespread use. Further developments will undoubtedly increase the scope of therapeutic endoscopy in human disease.

Obliteration of Esophageal Varices

The acute bleeding of esophageal varices is a common problem and a disorder for which the treatment remains controversial. Over the years many procedures have been advocated, including tamponade, ligation, portasystemic shunts, and splenectomy. The desire to avoid the high operative mortality associated with these techniques has generated new interest in non-operative methods.

One technique employs endoscopic evaluation and transendoscopic sclerotherapy. An initial assessment by flexible esophago-gastroscopy, is performed to identify varices and any active bleeding sites, and then under general anaesthesia, a flexible tubular sheath is passed down over the endoscope. This tube contains a hole or "window" near its distal end. As the sheath is introduced into the lower esophagus, varices protrude through the window into the lumen of the tube. A retractable needle passed down the endoscope. biopsy channel is advanced into the varix. A sclerosing substance such as ethanolamine oleate, is then injected into the varix. The needle is withdrawn and the sheath rotated both to compress the injected varix against the esophageal wall and to align another varix for injection. Varices near the gastroesophageal junction are injected first, followed by proximal varices. (fig. 14)

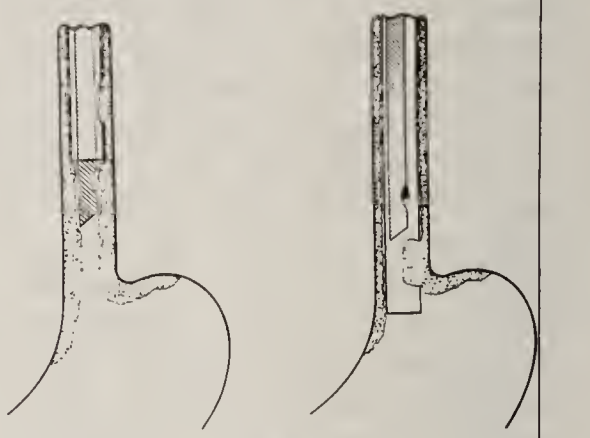


FIG. 14. Sclerotherapy of esophageal varices by transendoscopic injection.

This technique is employed both for immediate control and, with periodic injections, for long term management.

Results indicate that the overall survival (involving death from all causes) is not increased by this therapy. However, many studies are in progress and it is apparent that the survival of patients, who because of the extent of their disease are poor surgical candidates, is significantly increased by sclerotherapy, compared to control groups. Transendoscopic sclerotherapy quite possibly will become the treatment of choice for those with poor operative prognosis.

Extraction of Foreign Bodies

This area of endoscopic technique naturally lends itself to inventiveness and skill in the use of the instrument and accessories, and the literature contains many accounts of the successful manipulation of the esophagogastroscope in removal of swallowed objects.

In general, most swallowed foreign bodies will pass through the gut without difficulty. However, any sharp, pointed, bulky or impacted objects should likely be removed as soon as

possible, although impacted objects may spontaneously dislodge. An observation period can be employed for these lodged objects but extraction must be carried out if dislodgement does not occur.

Various forceps and loops have all been employed from time to time.

FIG. 15. Endoscopic forces grasping a coin

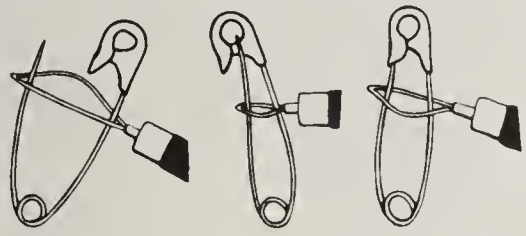


FIG. 16 Agile use of biopsy snare in safety pin removal.

One ingenious method for retrieval of a steel ball bearing from a child's stomach employed a "trawl net" technique using a latex contraceptive condom. The condom was tied to the endoscope with suture material and once the entire contraption had been passed into the stomach, the ball was "scooped". into the condom and pulled out. (fig. 17)

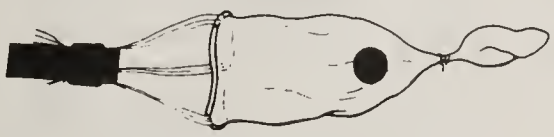


FIG. 17. Ingenious use of condom for ball-bearing retrieval

Lasers

The development and use of lasers have experienced an incredibly accelerated growth, having first been put into practical use in 1960 and medical use in 1970.

The laser beam (usually an argon laser) is transmitted along a quartz fiber which is encased in a catheter. This unit is passed down the endoscope biopsy channel. Under direct vision, the beam can be aimed by directing an attenuated beam toward the lesion and then the full power can be focused at the site of interest.

Although still in the developmental stages, several investigators have employed the laser for photocoagulation of bleeding gastric lesions in much the same manner as lasers are employed in ophthalmological surgery. At present, however, the equipment is expensive and controlled trials must be conducted before the value of this method can be accurately determined. However, it is the potential (especially in the area of treatment of acute GI hemorrhage) that such powerful instruments hold that encourage the further investigation and development of this field of therapuetic procedures.

Sphincterotomy and Stone Removal

Cholangiography and pancreatography as performed by endoscopic cannulation of the papilla of Vater are now routinely employed as aids to investigate biliary tract and pancreatic status. Fibreoptic duodenoscopy has also permitted the development of two procedures — sphincteromy and bile duct stone retrieval.

In the sphincterotomy procedure, the patient is sedated and a side-viewing dudodenoscope is passed into the dudoenum. Retrograde cholangiography is performed, then the diathermy wire is insterted into the papilla so that half the wire lies in the duodenal lumen.

The wire is tightened producing a bowing effect and stretching the sphincter and lower bile duct wall. Cutting current is applied to cut through the sphincter for a distance of approximately 15mm.

Complications can be severe (bleeding, perforation, cholangitis, and pancreatitis) and must be diagnosed and treated early.

Stone removal from the bile duct can then be undertaken. However, after sphincterotomy many stones will spontaneously pass or can be flushed out by irrigation of a T-tube placed during previous surgery. This conservative approach can be utilized, but must include a follow-up cholangiogram to ensure that the duct is clear. Later cholangiography can be greatly facilitated by leaving a biliary catheter in the duct during the sphincterotomy procedure. Baskets or balloon catheters are employed to remove stones either immediately after uncomplicated sphincterotomy or at a later date if the duct hasn't spontaneously cleared. (fig. 18)

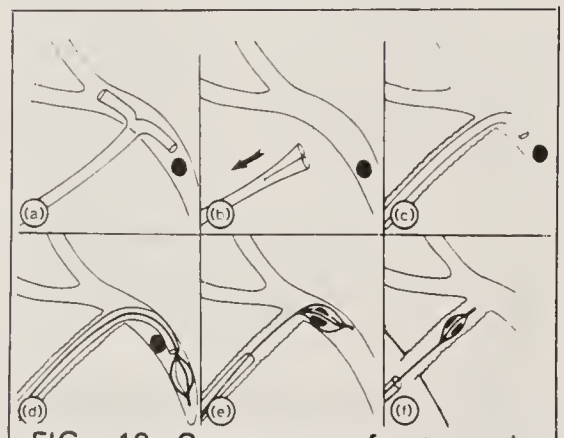


FIG. 18 Sequence of steps in stone removal

This method of treating biliary tract disease is ideal for the elderly and other high risk individuals for whom surgical hazards are too great. Undoubtedly as complication rates fall, more and more younger and lower risk patients will be treated this way.

Colonoscopic Polypectomy

This is a very easy procedure to perform and one which subjects the patient to no more discomfort than a barium enema.

Often polyps are seen on an radiographic study requested for an unrelated problem or found during colonoscopy performed for either another disorder or investigation of rectal bleeding. However, when polyps are found they should be removed and examined by the pathologist.

Complete colonoscopic examination should be performed even though polyps may be seen in

the lower colon. Polyps found are snared with a wire snare passed through the biopsy channel and controlled from the outside. Cutting current is applied to transect the polyp stalk and the polyp is retrieved by either forceps or the snare itself so that histopathologic examination of the polyp can be performed. Multiple polypectomy may be performed with no increase risk to the patient. Severe hemorrhage remains a real but uncommon complication. (fig. 19)

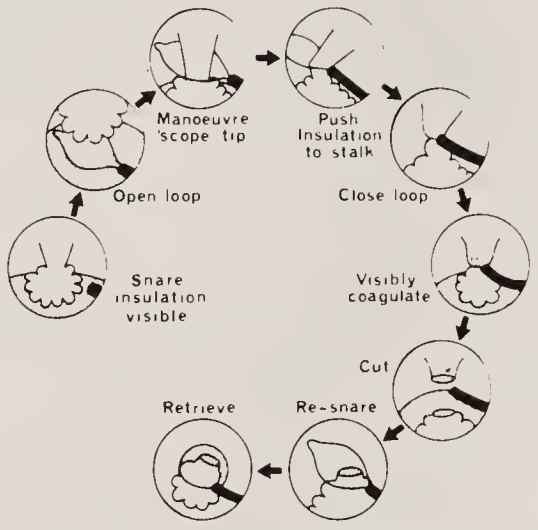


FIG. 19 Polypectomy sequence.

The role of colonoscopic polypectomy in prophylaxis of colonic malignancy is not clear. Certainly most polyps are adenomatous and few show either local or diffuse carcinoma in the polyp. The risk factors associated with progress along the polyp-to-malignancy continuum are not known but likely the adenoma-to-carcinoma pattern places those with either recurrent polyps or multiple polyps at higher risk of eventual carcinoma development.

The need for follow-up colonoscopy or radiologic contrast studies is individualized taking into account the patient's age, the histopathology of the initial lesions and their number.

Conclusion

This brief introduction to a few of the therapeutic modalities of endoscopy has illustrated the diversity of techniques available today or in the not-too-distant future.

It is fascinating to realize how recently the technology and skill of gastrointestinal endoscopy have been acquired, and yet how quickly endoscopy has established itself as both a diagnostic and a therapeutic tool in the management of gastrointestinal disorders. □

Acknowledgements

The author would like to thank Dr. H.S. Himal for his encouragement and assistance.

REFERENCES

1. Bailey, M.E. and Dawson, J.L. "Modified oesophagoscope for injecting oesophageal varices." *Br. Med. J.*, 2, 540, (1978).
2. Bennett, John Rd. (ed.) Therapeutic Endoscopy and Radiology of the Gut. Chapman and Hall, London, 1981.
3. Cotton, Peter B. and Williams, Christopher B. Practical Gastrointestinal Endoscopy. Blackwell, Oxford, 1980.
4. Coutsotides, T. *et al.* "Colonoscopy and management of polyps containing invasive carcinoma." *Ann, Surg.*, 188, 638-41.
5. Fruhmorgen, P. *et al.* "The first endoscopic laser coagulation in the human GI tract". *Endoscopy*, 7, 156-7, (1975).
6. Gilbertsen, V. "Rectosigmoidoscopy and polypectomy by sigmoid-rectal intussusception." *Br. Med. J.*, 1, 1395, (1974).
7. Hirshowitz, B.J. *et al.* "Demonstration of a new gastroscope, the fiberscope." *Gastroenterology*, 35, 50, (1958).
8. Hunt, Richard H. Colonoscopy: Techniques, Clinical Practice and Colour Atlas. Chapman & Hall, London, 1981.
9. Jackson, R.R. *et al.* "Adenomas of the colon the rationale for resection as the treatment of choice". *Dis. Colon Rect., 13, 47-58, (1970).*
10. Johnston, G.W. and Rodger, H.W. "A review of 15 years' experience. The use of sclerotherapy in the control of acute haemorrhage from oesophageal varices". Arch. Surg., 115, 476, (1973).
11. Kawai, K. *et al.* "Endoscopic sphincterotomy of the ampulla of Vater". *Gastrointest. Endosc.*, 20, 148, (1974).
12. Lawrence, B.H. *et al.* "Endoscopic laser photocoagulation for bleeding peptic ulcers". *Lancet*, 124-5, (1980)
13. Neslon, Robert S. Endoscopy in Gastric Cancer. Springer-verlag, Berlin, 1970.
14. Pacquet, K.-J. and Oberhammer, E. "Sclerotherapy of bleeding oesophageal varices by means of endoscopy." *Endoscopy*, 10, 7-12, (1978).
15. Rees, B.I. and Lawrie, B.W. "Non-operative removal of retained stones in the common bile duct." *Br. J. Surg.*, 65, 334-6, (1978).
16. Schindler, Rudolf. Lehrbuch and Atlas der Gastroskopie. J.F. Lehmann, Munchen, 1923.
17. Williams, K.G.D. and Dawson, J.L. "Fibreoptic injection of oesophageal varices." *Br. Med. J.*, 2, 766, (1979).
18. Wolff, W.I. *et al.* "Comparison of colonoscopy and the contrast enema in 500 patients with colorectal disease." *Am. J. Surg.*, 129- 181-6, (1975).
19. Wren, C. and Cockel, R. "Endoscopic removal of a swallowed ball bearing crom stomach of a four year old child." *Br. Med. J.*, 2, 252, (1978).

W.B. SAUNDERS COMPANY CANADA LIMITED

PUBLISHERS TO THE MEDICAL PROFESSION

One Goldthorne Avenue,
Toronto, Ontario
M8Z 5T9
Tel: (416) 251-3787

Chronic myelogenous leukemia

Charles Whelton 8T3

In recent years, much research has been devoted to clarifying the pathophysiology of CML. In this paper, recent findings are reviewed, and new information is presented, describing changes in membrane glycoproteins seen in this disease. Increased levels of sialic acid on cell-surface glycoproteins, with masking of terminal galactosyl residues, was found to be characteristic of untreated CML.

Chronic myelogenous leukemia is a disease which has long fascinated, and intrigued, clinicians and researchers alike. With its typical clinical picture, and specific chromosomal abnormality, this monocolonal malignancy is probably the most clearly defined of the myeloproliferative disorders.

Clinical and Hematologic Features

CML accounts for 20 to 30 percent of adult leukemias[24]. The disease is usually first diagnosed between the ages of 25 and 60, with no sex preponderance. Generally, patients with CML progress through two fairly well defined phases, a chronic phase followed by a blastic phase. Presenting symptoms in the chronic phase may be weakness, malaise, fever, weight loss, and, occasionally, easy bruising or bleeding. About twenty percent of cases are asymptomatic when first diagnosed. On examination, the spleen is almost always enlarged, sometimes massively so. Bony tenderness over the sternum is common.

At the time of diagnosis, the leukocyte count is usually near 200,000 mm^3 blood, the platelet count 400,000 mm^3, and the hemoglobin concentration about 11 gm/dl. Immature granulocytes abound in the peripheral blood; there is a direct correlation between the leukocyte count and the percentage of immature granulocytes in the blood at the time of diagnosis[26]. The bone narrow is markedly hyperplastic, with a predominance of myeloid forms, resembling the cells seen in the peripheral blood. Frequently, basophilia and eosinophilia are present. The Philadelphia chromosome is detectable in ninety percent of patients with the clinical picture of CML[46]. Leukocyte alkaline phosphatase is decreased or absent in the neutrophils of patients with CML at the time of diagnosis[32].

The chronic phase of CML usually can be well controlled by treatment and has a median duration of 34 to 39 months, when transformation to an accelerated or blastic phase occurs.

The blastic phase, known as blast crisis, represents an evolution from a stage of hyperplasia of mature elements to a stage with little myeloid differentiation, and, usually, increased numbers of myeloblasts and promyelocytes in the blood and bone marrow. This is accompanied by progressive anemia and thrombocytopenia, and by a lack of response to therapy[43]. In most cases, additional chromosomal abnormalities occur in the Ph-positive hematopoietic cells as blast crisis develops. In most cases, as well, the blast cells are similar to those of acute myelogenous leukemia. In twenty-five percent or more of blast crises, however, the immature forms can be classified as lymphoid, morphologically[4], cytochemically (by the presence of the enzyme terminal deoxynucleotidy[1] transferase)[23], and serologically (by the presence of the common ALL antigen)[22]. The blastic phase is terminal, and has a median duration of about ten weeks.

Treatment

The current treatment for the chronic phase of CML is generally effective in alleviating troublesome symptoms, by reducing the peripheral blood granulocyte count, and by causing regression of splenomegaly. Anemia is frequently corrected and thrombocytosis is controlled. Alkylating agents such as busulfan[30], or DNA synthesis inhibitors, such as hydroxyurea[25], lower the leukocyte count to a near normal level in about eighty percent of patients; the bone marrow, however, continues to show granulocytic hyperplasia, and the Philadelphia chromosome continues to be present in dividing marrow cells. Remission is hence incomplete, and treatment has little effect in preventing the development of blast crisis. Other

ALL - acute lymphocytic leukemia CML - chronic myelogenous leukemia FMLP - formyl-methionine-leucine-phenylalanine, chemotactic peptide
AML - acute myelogenous leukemia CSF - colony-stimulating factor Ph - Philadelphia chromosome PNA - peanut agglutinin, lectin.

modes of therapy used in the chronic phase of CML, including splenic irradiation[30], radioactive phosphorus[34], and splenectomy[49], are generally less effective in the chronic phase of CML than busulfan, and are infrequently indicated. Like busulfan and hydroxyurea, they are palliative and not curative.

A recent and exciting advance in the treatment of CML, which is potentially curative, has been to transplant CML patients with bone marrow from identical twins, after completely ablating their own myeloid tissue with very high doses of anti-leukemic therapy (cytotoxic drugs and total body irradiation). Preliminary results in twelve patients with chronic phase CML who underwent this treatment showed that the disease went into complete morphologic and cytologic remission in all patients[15]. One patient had a relapse two and a half years after transplantation, one died of interstitial pneumonia at four and a half months and ten have been in complete remission for periods ranging from nine to fifty-three months. Similar research is now being carried out at Princess Margaret Hospital in Toronto, where CML patients are being transplanted with bone marrow from HLA-matched siblings.

When blast crisis occurs, treatment is usually attempted using the same chemotherapeutic strategies as in the treatment of AML. These programs are much less effective in CML however[8], and death usually occurs in two to three months. Patients in whom the blast cells have lymphoid characteristics may respond more favourably to treatment with vincristine and prednisone[28]; half of these patients will enter a short term remission (with a median survival of twenty-seven weeks).

Pathogenesis and Pathophysiology

The evidence that CML is a monoclonal hematopoietic stem cell disorder comes from cytogenetic and isoenzyme studies. The Ph chromosome, found in ninety percent of patients with CML, normally arises due to a translocation from the long arm of one of the number 22 chromosomes, usually to the long arm of one of the number 9 chromosomes[39]. The Ph chromosome has been found in neutrophil, monocyte, erythrocyte, platelet, and possibly basophil precursors[11 19 14]. It is the only chromosomal lesion that is consistently found in a given neoplastic process, and is so specific that it is not unreasonable to hypothesize that it is involved in the pathogenesis of CML.

Further evidence of the monoclonal nature of CML comes from isoenzyme studies. In CML patients heterozygous for the X-linked enzyme glucose-6-phosphate dehydrogenase, only a single enzyme phenotype is expressed in the erythrocytes, granulocytes, monocytes, eosinophils, basophils, platelets[16], and possibly B-lymphocytes[29].

The specific etiologic factors that induce the genetic alteration in CML are unknown at the present time. There is little evidence that CML has a genetic predisposition (in contradistinction to AML); concordance of CML among identical twins is exceedingly rare[18]. Exposure to ionizing radiation seems to be implicated in the high incidence of CML among atomic bomb victims[20], and patients irradiated for ankylosing spondylitis[13]. A latency period of six to seven years occurs post-irradiation before CML becomes evident.

The capacity for phagocytosis in CML neutrophils has been reported to be decreased[47]; in busulfan-induced remissions, phagocytosis may return to normal[5]. Alkaline phosphatase levels may also be restored to normal during a busulfan-induced response[2]. Bactericidal capacity in vitro seems unimpaired in CML, when the peripheral blood granulocyte count is less than 90,000 mm^3 [35]. CML granulocytes have been found to enter inflammatory exudates[3]; using serum-filled skin window chambers, however, it has been shown that the granulocyte clearance rate from blood at sites of mechanical abrasion is fifteenfold lower in CML than in normals[1]. The clearance rate rises with therapy-induced remission.

The hyperleukocytosis during the chronic phase of CML is not caused by more rapid cell division of CML precursors[10]; intermitotic times for CML myeloblasts were found to be twice as long as seen for normal myeloblasts. The leukocytosis is thought to be contributed to, however, by (a) a decreased clearance of neutrophils from the bloodstream with an eightfold increase in intravascular survival times, when compared to normal neutrophils[9] (which is not explained solely by the presence of immature cells in the circulation[17], (b) marked expansion of the subpopulation of myeloid-committed stem cells, especially in the peripheral blood[33], (c) a reduced functional demarcation between bone marrow and blood, with the increased release of immature forms from the bone marrow.

The increase in the granulopoietic elements may be contributed to by regulator abnormalities. A key regulator of granulopoiesis in vivo is colony-stimulating factor (CSF), a substance produced by monocytes. During the chronic phase of CML, leukemic colony-forming cells seem to require CSF for proliferation, and show the same response to it as non-leukemic colony-forming cells[31]. Many CML patients have been shown to have widely fluctuating leukocytosis (5,000-500,000), with no treatment; in these patients, a preceeding parallel fluctuation in urinary CSF levels has been reported[12]. Elevated levels of CSF have been found in the urine of some CML patients[38]. Granulocytes normally produced lactoferrin, which inhibits CSF production by monocytes; CML granulocytes have recently been reported to produce significantly decreased levels of lactoferrin than normal granulocytes[6].

CML cells may gain a proliferative advantage by suppressing normal hematopoiesis. In vitro studies have shown normal

colony-forming cells to be inhibited both by CML neutrophils and by extracts from leukemic cells. The inhibitor has been characterized as a material of high molecular weight, that is capable of reducing the percentage of normal colony-forming cells in the S phase of the cell cycle[36].

Specific membrane abnormalities in CML neutrophils are not well documented. The alterations in phagocytosis, the diminished capillary emigration, and the premature myelocyte release from the bone marrow all suggest possible alterations in cell membrane adhesive or other functional receptors.

Preliminary data from our laboratory suggest the presence of characteristic surface carbohydrate abnormalities in CML neutrophils, which may play a role in the malignant behaviour of CML cells[42]. These data indicate that mature neutrophils in patients with Ph-positive CML are defective in their ability to adhere to column-packed nylon wool fibers, an in vitro test that closely parallels capillary margination in vivo[27]. This defect in adherence was partially reversed towards normal by pretreatment of the CML cells with Vibrio cholera neuraminidase, an enzyme that removes terminal sialic acid from surface carbohydrate chains. It might be thought that the cells which failed to adhere were the more immature myeloid forms; in our study it was the morphologically mature CML neutrophils which did not adhere to the nylon wool column. In contrast, cells from patients with benign leukocytosis (due to sepsis, for example) showed greater than normal adherence to nylon wool, which may reflect the rapid extravasation of these cells in vivo[9]. Adherence was not significantly affected by pretreatment with neuraminidase for normal neutrophils.

It was found that CML neutrophils reacted significantly differently from normal neutrophils in their ability to bind certain lectins. Peanut agglutinin (PNA), which specifically binds B-galactosyl residues, and limulin, which binds sialic acid residues, were seen to agglutinate CML neutrophils in proportions which were very different than seen with non-leukemic cells. Peripheral blood neutrophils from patients with untreated CML showed less agglutination with PNA than did normal cells, suggesting the presence of fewer accessible terminal galactosyl residues on CML neutrophils. The reverse occurred with limulin; several of the untreated CML patients showed increased agglutination with this lectin, suggesting an increased density (or accessibility) of cells surface sialic acid. Limulin agglutination of CML cells correlated inversely with PNA agglutination[42].

Polyacrylamide gel electrophoresis was used to further characterize cell-surface glycoprotein changes in CML. CML neutrophils were treated with galactose oxidase, an enzyme specific for terminal galactose and N-acetylgalactosamine on cell-surface carbohydrate chains; these oxidized sugars were then reduced with tritiated sodium borohydride. Surface glycoproteins were then extracted and electrophoresed, and labelled bands were visualized by fluorography (see Figure I) The major neutrophil cell-surface glycoprotein band (corresponding to a molecular weight of 120,000 daltons) showed decreased labelling in untreated CML neutrophils with this procedure, compared to normal neutrophils; this reduced accessability to galactose oxidase was reversible with neuraminidase pretreatment of the cells. Treatment of CML neutrophils with periodate, to oxidize terminal sialic acid residues, followed by reduction with tritiated sodium borohydride, resulted in increased labelling of the major cell-surface glycoprotein band, relative to normal neutrophils (see figure II).

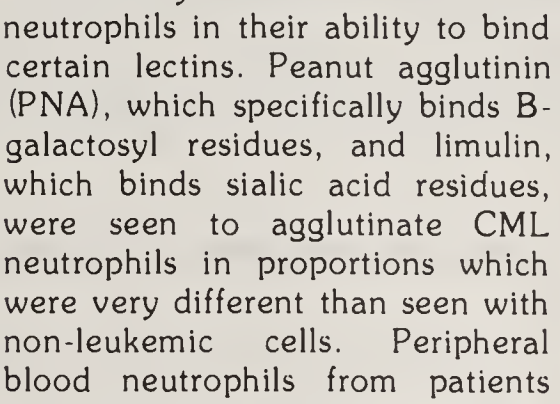


FIGURE I: Densitometric scanning patterns of galactose oxidase treated and tritium labelled granulocyte surface glycoproteins separated by polyacrylamide slab gel electrophores is and visualized by fluorography (CML-untreated CML patient, NL-normal)

The recent discovery that small synthetic N-formylmethionyl peptides, in particular N-formylmethionine-leucine-phenylalanine (FMLP), are strongly chemotactic[48 40] has greatly aided the study of neutrophil surface receptors, and their biomechanics. We have found reduced binding of ^{3}H-FMLP to untreated CML neutrophils, relative to normal cells. Binding increased after neuraminidase pretreatment of leukemic cells.

Our data on treated CML patients suggest that the receptor abnormalities of CML are reversible by maintenance busulfan therapy in some patients.

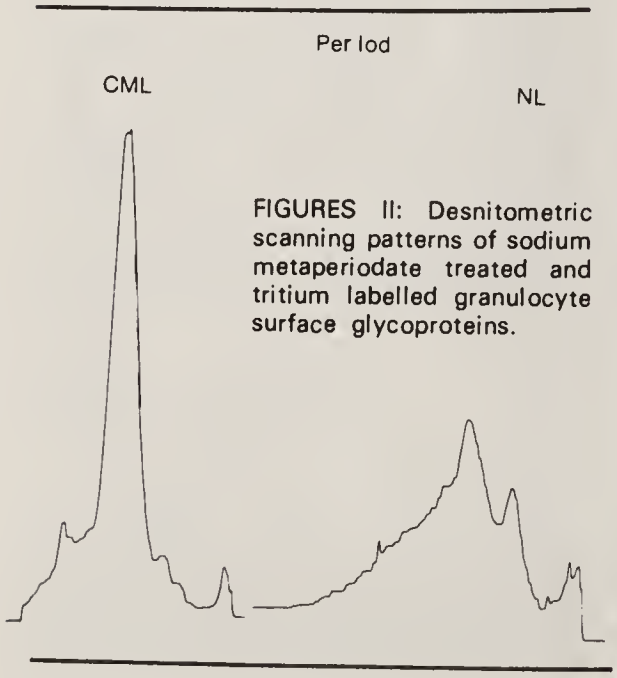
These data suggest that ectopic sialic acid or hypersialylation of glycoproteins on the surface of CML cells, by masking receptors (possibly involving galactose) mediating granulocyte-substrate adhesion, and capillary emigration, may contribute to the leukocytosis seen in this disease. It might also be speculated that the masking of galactose, or other surface carbohydrate residues, with a resulting disruption of surface receptors, could influence the maturation of neutrophils in CML, and mediate their premature release from the bone marrow. It is to be noted that increased levels of sialyl transferase as well as other glycosyl transferases have been described in AML[40]; CML remains to be studied in this regard.

Cell-surface oligosaccharide changes in other malignant processes have been extensively documented in recent years. It may be relevant to the changes noted above for CML that cultured cell

lines from hamsters, mice and chicks, transformed by DNA or RNA viruses were shown to have increased amounts of glycopeptides containing unusually high amounts of sialic acid, in pronase-digested membrane trypsinates of these cells; these changes were independant of species, and transforming agent[7] [44]. Similar glycopeptides were also found in certain hepatoma cells[44], mouse mammary tumours[41], and human lymphoblastic and myeloblastic leukemia cells[45]. It has been shown that the ability of murine tumour cells to metastasize spontaneously from subcutaneous sites is positively correlated with cell surface sialylation, in particular the degree of sialylation of galactosyl and N-acetylgalactosaminyl residues in cell surface glycoconjugates[50].

Several laboratories have demonstrated the importance of regulated changes in cell-surface carbohydrates during cells development and maturation. As normal intestinal epithelial crypt cells mature and are translocated upwards from the bottom of the crypt they show increased sialyl transferase activity[21]. Similarly, ninety percent of immature thymocytes found in the mouse thymus possess surface galactosyl determinants which become fully sialylated in circulating peripheral blood T-lymphocytes[37].

It is clear that several biochemical and physiological abnormalities occur concurrently in CML. At the present time, which abnormalities are important and which are not remains unknown.□



FIGURES II: Desnitometric scanning patterns of sodium metaperiodate treated and tritium labelled granulocyte surface glycoproteins.

Acknowledgement:

Research was done at the Leukemia Research Laboratory, Toronto Western Hospital, director Dr. Michael Baker. Thanks to Joseph Lee, Gordon Hyland, Susan Cane, Virgilio de Leon, and, especially, Amita Kanani and Dr. Baker.

References available upon request.

THE UNIVERSITY OF TORONTO
MEDICAL
BOOKSTORE

Textbooks for all subjects.
Comprehensive reference books
and general interest titles.
Complete review manuals
in Medicine and Nursing.

• **ask for our free catalogue**
• **no-charge student charge accounts**
• **free special order service**

The Medical Bookstore is open
Monday through Friday 8:45 am til 6 pm
Saturday from 11 am til 5 pm

The MEDICAL BOOKSTORE
is located in
The UNIVERSITY BOOKROOM
63A St. George Street, Toronto
978-6161

The Medical Student's Niche in the Hospital Setting: What Price Education?

Richard Hegele 8T4

There is without doubt an absolute necessity for the medical student to have exposure to patients as a part of his training. No one would dare call a graduate of a medical programme "prepared" to competently deal with human life if his knowledge were derived exclusively from text-books, lectures, laboratory sessions and seminars. The so-called "teaching hospital" professes to be an institution wherein patients serve as "teaching material" for students and staff in exchange for presumably superior quality care from presumably superior quality physicians and surgeons. Whether or not this aspiration is fulfilled in reality is open to debate; however, let us assume that the idea situation exists and that medical students have access to such an environment for the purposes of increasing their academic knowledge and developing their practical skills. Once within a teaching hospital, should a medical student be given free rein to roam about interrogating patients and performing a variety of physical maneuvers (often unpleasant to the recipient) in the name of his medical education? Do patients truly "belong" to the hospital (and thus to students)? Does not the student have obligations to anyone in the hospital setting other than himself? What, if any, responsibilities does the medical student have to the patient? To the hospital staff? What if there exist conflicts between the goals of the patient and those of the institution? Are they resolvable? Through a presentation of two realistic scenarios, it is hoped that a springboard for thought about these issues will be provided.

The hospital setting may be considered, for the purposes of this paper, to consist of three basic types of mutual relationships: the doctor - patient, the doctor - student and the student-patient. Each of these interactions is fraught with a variety of objectives, tensions and intricacies. For example, the doctor-patient relationship may, from the latter's standpoint, be concerned with such goals as the procurement of essential health services, the ensurance of adequate monitoring of his condition, and the receipt of compassionate, holistic-oriented therapy. The physician, on the other hand, perhaps may be interested in the patient as a research subject or a teaching object for students once the necessary care has been instituted or guaranteed. The student, realizing the similarities and differences between the aspirations of doctor and patient, is often caught in the middle of a tug-of-war in which only through making allowances and adjustments in his behavior can he hope to satisfy their desires, as well as his own.

What can be involved in the supposedly "tame" situation where a clinician brings six eager medical students to the bedside and authoritatively blurts, "Mrs. Smith, I have some young doctors here to see you. Will you let us have a few moments of your time?" Consider some admittedly contrived yet plausible points of view held by the various parties:

(a) **The clinician:**

Mrs. Smith, your liver is enlarged from consuming too much ethanol and you've got ascites. For the time being, your basic needs are well looked after, so why don't *you* do *us* a favour now? These eager young medical students - I called them "doctors" to make it more acceptable to you to put up with what I've got planned - would just love to learn how to recognize a fluid-filled peritoneal cavity, so I'm going to let all six of them examine your abdomen and "learn the ropes", so to speak. Oh, they might be rather clumsy, for this is the first time they've ever done anything like this, but I'm sure you won't mind.

(b) **The patient:**

Doctor, the stupid fool in the bed next to me was snoring all last night and I think I slept a grand total of 25 minutes. This is the fourth group of "young doctors" I've seen this week and frankly, I'm sick and tired of getting my abdomen thumped. Why won't you let me rest in peace?

(c) **The student:**

Why did he call us "doctors"? We haven't earned our degrees yet. Perhaps it's just an unconscious thing. It's obvious that the lady is not at all thrilled to see us. But, *she's* got the hepatomegaly and the ascites, and we've got to learn how to detect it, so then it's *justifiable* to go

through with the examination of her abdomen.

In this instance, not one participant feels overly pleased, yet in the end, the examination is performed. This is not to say that there do not exist medical students who copiously salivate upon being referred to as "doctors" (albeit "young" ones), and that every patient despises being examined; but, it is clear that differences in expectations amongst the parties may lead to misunderstandings and potentially ugly scenes. Should the medical student make a contribution to the avoidance of such problems, and if so, what can he do? If one pauses to consider the issues at hand, it becomes clear that it is not enough for the student to act passively and thus avoid confrontation, for by doing so he will be showing his disrespect toward the privilege of being in the teaching hospital in the first place, and, from a more egotistical standpoint, he may well be compromising his own medical education. Consider the student's dilemma: he is caught in a web of tensions between furthering his knowledge, practising on a less-than-willing subject, maintaining the "integrity" of the medical profession by obeying his clinician, justifying the obvious deception involved in being called a "doctor", all whilst attempting to maintain a semblance of professionalism. Surely this cannot be a context which is conducive to "ideal" learning. At the very least, the medical student owes it to himself to srive for the best possible educational environment, and if he makes an effort in this direction, he stands to benefit greatly.

What can the student actually *do*, all things considered? He may wish to approach the clinician privately and inquire as to why he was called a "doctor". In this manner, the student avoids making a scene in front of the patient, thus contributing to the "unity" and "integrity" of which the medical profession prides itself. Although he runs the risk of being callously thrown out of the physician's office if the chat does not proceed well, it must be borne in mind that practically any potentially beneficial procedure is associated with some probability of failure, whether it be coronary bypass surgery or asking the clinician to refer to students as "students".

As far as the student's approach to the patient is concerned, a sincere "thank you" uttered at the conclusion of the examination may be all that is required to remind both the patient and himself about how valuable the subject's time was in his educational enrichment. Through such a simple gesture, the student has appreciated the fact that a patient is a human being and thus something beyond an inanimate teaching aid. In short, the student has "humanized" his medical education.

Having cast the medical student in the role of diplomat, it is perhaps worthwhile to examine the limits to which he can put his talents to use. Consider the following situation: A terminal cancer patient who is unaware of his diagnosis has just agreed to spend some time with a medical student. Over the next ninety minutes, the student performs a thorough history and physical examination. During this time the patient has volunteered a vast amount of "private" information (which is the medical student's job to extract). In addition, he has agreed to allow the student to perform a rectal examination amongst other pleasantries. At the conclusion of the session, the patient demands, "What's my diagnosis and what's my prognosis? I've let you ask me all these questions and perform all these maneuvers—the least you can do is tell me what's going on."

Is it part of the medical student's role to honour this patient's desire? If one looks at the situation from an "unemotional", abstract perspective, then it is conceivable that the student should indeed tell the patient what is requested because it is part of the educational process to learn how to inform such patients of their impending demise. If one accepts this viewpoint, he is making a grave error because he is confusing the difference between the enhancement of his education and the privilege of being educated in a hospital setting. No medical student has the "right" to see patients as a part of his training. There are no such guarantees entrenched in a tuition fee payment. Patients do not generally go into hospital for the purpose of seeing medical students; when they do see students, they are in effect admitting to their compromised state. Medical students should not take advantage of "pouncing" upon these unfortunate souls; rather, they should appreciate how lucky they are to even have the opportunity to see patients. As described at the commencement of the paper, the incorporation of patient contact into the curriculum helps to ensure adequate training for the future physician, but it is nothing more than that. Thus, medical students, having no diplomas or authority, have no business in giving diagnoses or prognoses. There are doctors who are well-compensated by the provincial government to do these things. The student should not exceed his role. At best, he could thank the patient for his time and with regret say that he is in no position to answer such questions, adding that the patient's doctor(s) must assume this responsibility.

The two scenarios discussed in this paper have attempted to illustrate some of the things a medical student can or cannot do in a teaching hospital environment. In one, he was cast as a hero of sorts; in the other, as something substantially less. In any interpersonal contact, there are invariably going to be some areas of disagreement and differences in objectives between the parties involved. The medical student, instead of complaining and whimpering about these tensions, should take positive steps in dealing with them. Not only will he also acquire a "feel" which distinguishes the physician from the well-tuned

(Continued on pg. 151)

Water Fluoridation: Political Aspects of the Implementation of a Public Health Measure

Anne Curtis, 8T2

Increased levels of fluoride in the water were first discovered to correlate with decreased prevalence of dental caries over 40 years ago. Studies were then done supplementing municipal water supplies with fluoride, which showed that the prevalence of caries in the children exposed to the fluoride while their teeth were developing could be decreased by over 50% Later studies indicate that these benefits extend into adulthood and help prevent root caries as well. Dental fluorosis is not a problem at the level to which municipal water supplies are supplemented, 1.0 - 1.2 qpm, but does become progressively more severe at levels higher than this. Allegations that an increased incidence of cancer, Down's syndrome, allergies, and renal disease may be associated with water fluridation remain unsubstantiated. The measure is endorsed by all major scientific and regulatory bodies as safe, efficacious, and cost-beneficial.

Evidence is presented that only 37% of the Canadian population have fluoridated water, and there has been little or no improvement in this figure in the past decade. The number of fluoridated communities is actually decreasing, from a high of 481 in 1973. Provincial legislation affecting fluoridation is reviewed in this paper, and an analysis is made of some of the factors which result in the fact that the majority of referenda on the subject are won by anti-fluoridationists. A major section of the paper deals with the tactics which are recommended for pro-fluoridationists to use in conducting a successful referendum campaign.

The scientific arguments favouring water fluoridation are well established, and it is now time for health professionals and government to take the political steps necessary to ensure that this important public health measure is implemented.

The Efficacy of Fluoridated Water in Preventing Dental Caries

The discovery that fluoride was beneficial in decreasing the prevalence of dental caries was an accidental one, and makes both an interesting story and a useful illustration of the role of epidemiology in public health. H.T. Dean, in the 1930's, was investigating the high prevalence of mottled, discoloured teeth in certain communities, whose neighbouring communities had normal dental health. He found that the affected communities obtained their water from a common source, different from that of their healthy neighbours. Later it was found that water in the affected communities had extremely high fluoride levels, not shared by their neighbours. At this point, though, interest was drawn to the fact that the affected communities also had significantly fewer dental caries than their neighbours. Dean[9] then studied children in 21 US cities and found that caries prevalence decreased as water fluoride levels increased 1.5 ppm was found to be an upper limit beyond which mottling increased without corresponding decreases in caries prevalence. 1.0 ppm fluoride seemed optimal, with decreases below this resulting in increased caries prevalence.

This discovery prompted initiation of controlled fluoridation programs in the 1940's in Brantford, Ont. Newburgh, N.Y.; Grand Rapids, Mich.; and Evanston, Ill. All these studies showed substantial reductions in caries (Table 1[4]). Brantford's water was supplemented with fluoride to levels of 1.0-1.2 ppm in 1945. Ten years later[2] caries experience there was compared with that in Stratford, whose water was naturally fluoridated to 1.6 ppm, and that in Sarnia, whose water was essentially fluoride free. By 1955, as shown in Table I, the Brantford children were showing significant caries reduction, and resistance to decay was becoming comparable to that in Stratford. There were also more caries free children as compared to Sarnia. By 1963, 16-17 year-olds from Bratford, who had spent their whole life in the fluoridated community, had over 50% fewer caries, and 12% were caries free, compared to .4% in Sarnia[3]. Neither Brantford nor Stratford reported dental fluorosis or adverse health effects. D.W. Lewis[17] reviewed school dental surveys done in Toronto from 1963, when fluoridation was introduced, until 1975.

TABLE I PERCENT OF DMF TEETH PER CHILD BEFORE AND AFTER FLUORIDATION

Community	Age	DMF Teeth Per Child	Percent Difference
Brantford, Ont.			
Before F (1944–1945)	8	2.4	
After F (1955)	8	1.1	54.2
Grand Rapids, Mich.			
Before F (1944–1945)	10	4.9	
After F (1954)	10	2.3	53.1
Newburgh, N. Y.			
Before F (1944–1945)	9	3.1	
After F (1954)	9	1.5	51.6
Evanston, Ill.			
Before F (1946)	12–14	9.0	
After F (1959)	12–14	4.6	48.9

Adapted from United States Public Health Service statistics

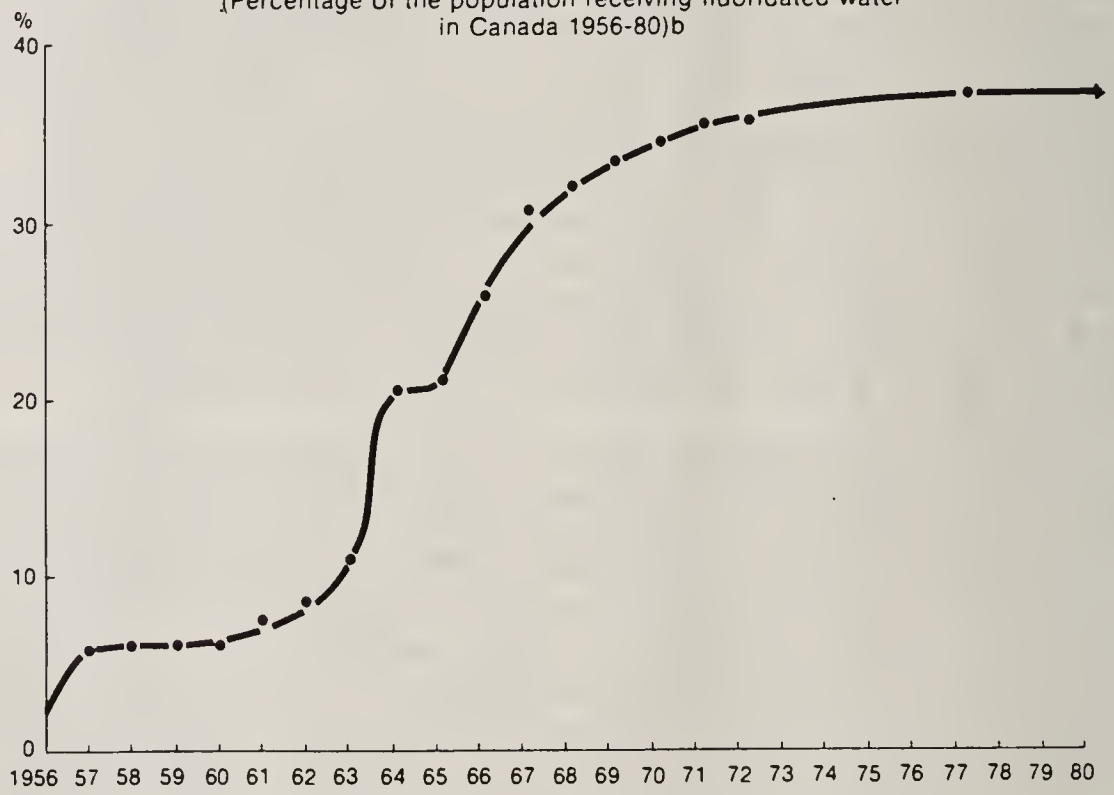
The improvement in dental health became more marked as the study went on and children had been exposed to fluoride during development, still had a 33-36% reduction in caries. Less than 5% had tooth mottling, and this was mild.

Other studies done on adult dental health, generally in naturally fluoridated areas where it is possible to find individuals who have consumed adequately fluoridated water from birth to old age, have confirmed that this dramatic reduction in caries compared to non-fluoridated areas persists into old age. It becomes less dramatic with increased age because periodontal disease causes tooth loss independent of the fluoride concentration in the water supply. The DMF index of decayed, missing, and filled teeth is the most widely accepted measure of caries experience in a population and indeed in children missing teeth are generally due to caries, though trauma or othodontic removal have to be considered. In older people missing teeth are often due to periodontal disease, though loss due to caries still occurs. In the past 20 years there have been significant declines in edentulousness in all age groups, meaning that adults are at risk for caries longer. Periodontal disease often results in exposure of the roots of the teeth so that root caries, which are difficult to treat, are an increasing problem. Stamm and Banting[24] have shown significant reductions in root caries and fillings at all ages in lifetime residents of fluoridated communities. There is a suggestion, as yet unproven, that since the cementum of roots of teeth continues to be modified throughout life, as opposed to tooth enamel, which incorporates fluoride chiefly during development, drinking fluoridated water, even for adults who were not exposed to it as a child, may be beneficial in reducing root caries.

FIGURE I

GROWTH OF WATER FLUORIDATION

(Percentage of the population receiving fluoridated water in Canada 1956-80)b



a. Toronto's water supply was fluoridated.

b. Data from 1956-77 from Fluoridation in Canada, 1956-72 and December 31, 1976

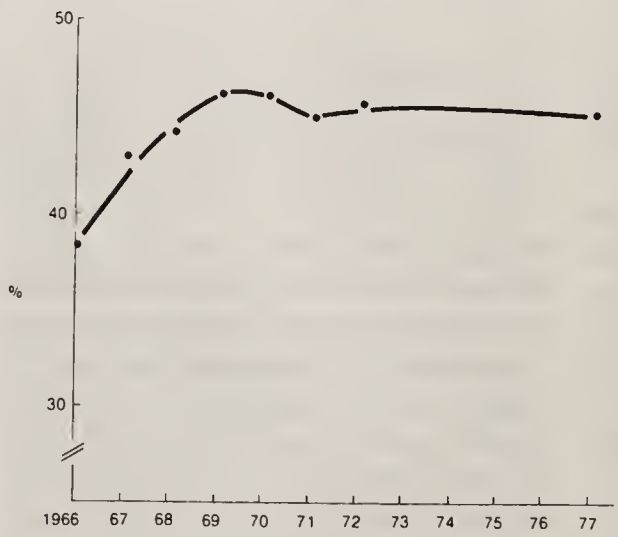


Figure II Growth of water floridation (Percentage of the population on potable water systems receiving fluoridated water in Canada 1966-77)

Fluoridation in Canada, 1966-72, December 31, 1976, 1980 data not available.

TABLE II

CONTROLLED FLUORIDATION IN CANADA BY PROVINCES
1962-1980

	Population Served					
	1962 *	1965 *	1968 *	1973 *	1977 *	1980 **
Newfoundland	0	12.500	7,108	37,748	49,735	44,253
P. E. I.	0	0	0	20,843	20,843	22,073
Nova Scotia +	169.500	208.700	270,625	288,811	332,155	348,763
New Brunswick	0	0	0	79,000	82,623	88,159
Quebec	166,400	295,500	519,763	719,784	753,628	1,101,750
Ontario	354,300	2,546,700	3,766,731	4,633,577	5,063,219	5,142,558
Manitoba	531,100	555,600	585,406	647,538	665,688	688,321
Saskatchewan	214,700	269,300	299,108	335,479	330,630	301,199
Alberta	33,100	72,400	476,937	580,703	767,481	765,515
British Columbia	56,300	76,100	120,400	206,536	287,099	324,135
Yukon Territory +	4,900	5,100	4,620	9,500	11,600	13,781
Northwest Territory			12,992	15,959	18,472	19,280
Canada	**1,535,300**	**4,050,100**	**6,063,690**	**7,575,478**	**8,383,373**	**8,859,787**

• From Fluoridation Status Reports, 1962-77.
• • Population projections based on percentage change of population 1971-76. Canadian Year Book. 1978-79, Minister of Industry. Trade and Commerce, 1978.
+ 1980 date unavailable, figures based on 1977 figures from Fluoridation in Canada, as of December 31, 1976, using 1980 population projections.

TABLE III: Provincial Legislation on Fluoridation

Province	Fluoridation Mandatory	Local Option	Plebiscite Required	Provincial aid to offset cost
Newfoundland	x	+	except St. John's	+
Prince Edward Island			except Charlottetown	x
Nova Scotia	x	+		x
New Brunswick	x	+		
Quebec	x	+	x	Recently rescinded due to lack of interest
Ontario	+	N/A	N/A	+
Manitoba	x	+	If 10% of voters sign petition	x
Saskatchewan	x	+	x	100%
Alberta	x	x	x	x
British Columbia	x	+	+	Up to 50% if have municipal debt Help in training and monitoring
Yukon Territory	x	+	If 40% voters sign petition	
Northwest Territories	x	Small communities and non-potable water systems.		
	x	Small communities and non-potable water systems.		

Adverse Health Effects of Excess Fluoride

Dental fluorosis is a universally recognized adverse effect of excess fluoride. Dean's classification[16] describes and scores the enamel changes in the various stages of dental fluorosis. Each tooth is rated into one of the six categories and the person's dental fluorosis score is the highest score recorded for 2 or more teeth. The degree of dental fluorosis in a community is obtained by multiplying the individual scores by their frequency distribution. Residents where fluoride levels are 1.2 ppm or less are usually normal, though a few may have mild fluorosis. Note that enamel opacities are also found in non-fluoridated communities, sometimes more frequently than in communities fluoridated to 1.0 ppm, and may be impossible to distinguish from mild fluorosis. At 2.0 ppm a few individuals may develop moderate fluorosis, and at 3.0 ppm a few may develop severe fluorosis. With levels over 3.0 ppm the percentage of people with severe fluorosis increases significantly. Note that dental fluorosis is based on daily intake of fluoride, so it depends on the amount of water drunk as well as the concentration of fluoride in the water. People living in cooler areas drink less water, and so require a greater fluoride concentration in the water which they consume.

Skeletal fluorosis, consisting of hypermineralization of bone, calcification of ligaments, and bony outgrowths, has not been observed even in communities with 20.0 ppm fluoride in their water. Symptoms are pain in the joints of the hands, feet, and spine, and later a stiff spine with limited motion. Acute fluoride poisoning, that is, a lethal dose of 5-10 grams of NaF, blocks normal cells metabolism and causes diffuse ab-

dominal pain, diarrhea, vomiting, and painful limb spasm.

Dr. John Yiamouyiannis, Ph.D., and Dr. Dean Burk, Ph.D., are two major anti-fluoridationists working for the National Health Federation. Dr. Yiamouyiannis[25] compared crude mortality rates from cancer in 10 large American cities which were fluoridated in 1950, to similar rates in 10 unfluoridated cities over the period 1950-1970. He produced a graph showing that the cancer rates in the fluoridated cities were increasing more rapidly than in the unfluoridated cities over that time period. Doll and Kinlen[12], prominent cancer epidemiologists at Oxford, subsequently reanalyzed this same data, calculating the expected rates of cancer for each city based on the age, sex, and race of the population at several points over the 20 year period, since shifts of population were occuring, and compared these to the observed rates at each point in time. This analysis showed that the observed rate of cancer had decreased relative to the expected rate in the fluoridated cities, and the ratio had remained the same in the non-fluoridated ones. Numerous studies have been done since, and failed to show any connection between exposure to fluoridation and cancer of any site, heart disease, intracranial lesions, nephritis, or cirrhosis of the liver. In 1977 the Department of National Health and Welfare published an analysis of Canadian drinking water fluoridation and cancer mortality data over the period 1954-1973[10]. They concluded that:

"No appreciable differences in death rates from all types of cancer or any specific tumour site were indicated between fluoridated and non-fluoridated municipalities over this period. Nor were any significant differences apparent between death rates from all types of cancer when compared within the same group of municipalities prior to and after fluoridation."

Two studies by Rapaport originally suggested that fluoride could have a dose-related causal effect on Down's syndrome. Both studies had obvious design flaws casting doubt on their credibility, the first[21] because mothers were classified by their place of delivery not their place of residence, so data on the amount of fluoride the mothers were exposed to wasn't properly obtained. In the second study[22] he reported far fewer cases of Down's syndrome than are expected in any population, suggesting inadequate case finding and hence incomplete data. Three studies done since, separately, by Berry[1], Needleman[19], and Erickson[13], have failed to show any connection between fluoridation and Down's syndrome or congenital malformations.

Isolated researchers have suggested that allergy or intolerance to fluoride occurs in a small percentage of the population. Indeed, in an industrial setting, sensitization does appear to occur, with dermatitis in the very sweaty parts of the body. Sensitivity has not been a problem among the 100 million Americans drinking fluoridated water, those exposed to sea water, which is 1.4 ppm fluoride, tea drinkers, children on supplements, or those receiving methoxyflurane anesthesia, however. The American Academy of Allergy[14] unanimously declared that "there is no evidence of allergy or intolerance to fluorides as used in the fluoridation of communal water supplies."

Finally, comparing communities with 8.0 ppm natural fluoridation to unfluoridated communities has failed to show an increased incidence of renal disease. Since the ion is excreted renally, however, those with diabetes insipidus and impaired renal function may accumulate it, and those with renal failure on dialysis are generally given fluoride free dialysate to help remove it.

In 1961, the Ontario committee[20] which had been appointed to inquire into and report upon the fluoridation of municipal water supplies published its conclusions that:

vi. "We are convinced that it has been conclusively proved that the presence of fluoride, either naturally occurring or mechanically added in a municipal or communal water supply in concentrations of approximately one part per million strikingly reduces the incidence of dental caries when such water is consumed during the period of tooth development and that the caries-reducing effect of fluoride extends into adult life."

vii We are also convinced that the long-term ingestion of fluoride at approximately one part per million over a very wide range of water intake is not harmful to bodily health and that no fluorosis of esthetic significance is specifically associated with it."

The Cost Effectiveness of Water Fluoridation

The cost effectiveness of adding fluoride to drinking water in order to prevent dental caries is undisputed. The annual per capita cost varies with the size of the community, since much of the cost consists of capital expenditure at the outset to buy fluoridation equipment, and also varies with the water source and the type of fluoride used. To fluoridate the 96.7 billion gallons of water used in Metro Toronto every year costs $268,000. Based on the 1976 census which said Metro Toronto had 2,803,101 people, this would be an annual per capita cost of 9.56 cents (This cost is slightly over-estimated because 1981 costs are being used for a 1976 census, and the population may well have been larger in 1981). If the current recommendation to increase Metro's fluoride level from 1.0 ppm to 1.2 ppm, based on a correction for decreased water consumption in cooler climates such as Toronto's, the cost will rise to $318,000. Other cost figures quoted are $1.80/person/year in very small communities of about

250 people, to 15c/person/year in very large cities. The cost benefit ratio is estimated to be 1:50. In many provinces communities are eligible for grants to help offset the cost of fluoridation. As the Ontario committee[20] which studied the issue in 1961 concluded:

> x "We find that the cost of fluoridating a municipal water supply is very reasonable in relation to the health benefit to the community."

The Implementation of Water Fluoridation

Having established the safety, efficacy, and cost benefits of water fluoridation, it is now pertinent to review worldwide and Canadian experience with the implementation of this public health measure. In the Unites States as of Dec. 31, 1975[16] 49.4% of the population was drinking fluoridated water, 11 million naturally so and 95 million supplemented with fluoride. Eight states plus Puerto Rico had mandatory fluoridation for all communities of a certain minimum size. On the other hand, 28 states had less than 50% of their population drinking fluoridated water, 13 of the 57 cities with populations over 250,000 were unfluoridated, and of the 6 largest cities, Los Angeles remained unfluoridated.

Worldwide, only the Republic of Ireland has legislated national fluoridation. More disturbing is the recent trend which has halted the growth of fluoridation, and led to its elimination in some areas. Sweden, in 1971, and the Netherlands, in 1976, abolished fluoridation, whereas their previous laws had favoured it. Statewide referenda to prohibit fluoridation were held in Oregon, Washington, and Utah in the 1970's. While prohibition was defeated in the first two states, it passed in the third.

Here in Canada, growth in the percentage of the population receiving fluoridated water has come to a virtual standstill since the early 1970's (Figures I and II[4]) 37% of the population, and 46% of those with potable water systems receive fluoridated water. The actual number of communities supplied has been decreasing since a high of 481 in 1973[4]). Montreal, Calgary, Vancouver, and 8 other metropolitan areas are still unfluoridated. In Ontario Kitchener, St. Catherines, Thunder Bay, Sault Ste Marie, Cambridge, Guelph, Niagara Falls, and Kingston do not fluoridate their water.

Table II[4] shows the population, broken down by province, with controlled water fluoridation in each of six census reports between 1962 and 1980. As discussed before, the rate of growth has dropped off sharply, and the fluoridation of Quebec City in Dec., 1978 accounts for most of the increase since 1977. There has also been some increase of the population in previously fluoridated areas. Newfoundland, Saskatchewan, and Alberta, all had an absolute decrease in the number of people drinking fluoridated water between 1977 and 1980. Table III[4] shows 1980 figures of the number of people in each province with both controlled and natural fluoridation, and lists the provinces in descending order of percentage of population served.

Another concern is inadequate fluoride levels in "fluoridated" communities. The data on this is poor, but many local officials are concerned about it and the importance of a liason with the waterworks operator to make sure he understands the importance of his role can not be underestimated.

Provincial Legislation affecting Water Fluoridation

> "The Canadian Dental Association (CDA), recognizing its commitment to a renewed fluoridation initiative in North America and acknowledging its responsibility of leadership to the dental profession in Canada, strongly reaffirms its position on fluoridation of public water supplies... Exhaustive scientific research and the experience of people throughout the world reveal fluoridation to be an efficient, safe and inexpensive public health procedure. There are no alternative methods of equal effectiveness."[7]

Given such unequivocal support from the dental profession, echoing the support given by the Ontario committee which had reported 20 years previously, it is of great concern that nearly two-thirds of the general public are still drinking unfluoridated water, and the number of fluoridated communities is actually decreasing. Table VIII[4] gives a summary of the water fluoridation legislation in each province. Note that Quebec is the only province with mandatory water fluoridation. This legislation was passed in June, 1975 with a deadline for adherence of Dec. 31, 1978. There has been strong opposition from the Mayor of Montreal, Jean Drapeau, and from the provincial Ministry of the Environment whose "Quebec Report" has allowed anti-fluoridationists to obtain media coverage. The legislation remains controversial, and Montreal remains unfluoridated. In April, 1977, Quebec also enacted a plan to administer fluoridation.

Ontario's legislation has several features which hamper fluoridation efforts. First, only 10% of the voters need to sign a petition to force a plebiscite , and it is not difficult to get that number of signatures. Second, if the fluoridation plebiscite is successful another can be forced immediately just by collecting another 10% of voters signatures on another petition. Third, the wording for referenda is laid down by the provincial government and is confusing because it contains a double negative-"Are you in favour of the discontinuance of water fluoridation..." "No", therefore, means you wish fluoridation to continue.

The legislation in Alberta and British Columbia is particularly based against fluoridation. In Alberta a plebiscite is mandatory, and as will be discussed later, it is much more difficult to win a plebiscite than to persuade a local government to implement fluoridation. If the fluoridationists lose the plebiscite, they must wait another 2 years to try again, but if

they win, there is no legal requirement for the local authorities then to implement fluoridation. In British Columbia 60% of the voters must favour fluoridation in order to win a plebiscite, and this is extremely difficult to achieve.

The Political Realities of Winning Public Referenda on Fluoridation

In U.S. opinion polls conducted between 1959 and 1977[4] 51-70% of those surveyed favoured fluoridation, only 10-15% were opposed, and the rest had no opinion or felt they needed more information to decide. Yet, of the 900 referenda held in the United States between 1955 and 1965[16], almost two-thirds were defeated. Only 7% were opposed, and the rest had no opinion or felt they needed more information to decide. Yet, of the 900 referenda held in the United States between 1955 and 1965[16], almost two-thirds were defeated. Only 7% of the 6795 localities in the U.S. which had controlled fluoridation in 1975 had been authorized as the result of a referendum, the rest had been authorized by local government. Interesting sociologic issues are raised when one attempts to analyze why a public health measure which is unanimously and firmly endorsed by the professions concerned, and which on the surface has a broad base of public support, seems unable to make progress in implementation, and repeatedly loses in referenda.

The reaction of the scientific community to this apparent paradox was, predictably, to commission studies to characterize opponents of fluoridation. The opposition was found to be linked to antiscientific and anti-intellectual attitudes, ambivalence toward science and technology, and resentment of government. C.T. Shaw[23] found that anti-fluoridationists tended to be in low-paying occupations, over 40, and either unmarried, or with no children under 12. Anti-fluoridationists are able to capitalize on several contemporary trends. Concern about the environment, and about food additives and pollution can be used as an argument against fluoridation. Government, big business, and science, have lost credibility with failures such as urea formaldehyde foam insulation, Swine flu immunization, and Three Mile Island fresh in the public's memory, so their endorsement no longer sways an electorate.

The civil rights issue is whether the whole community's drinking water should be fluoridated when consent is not unanimous. The courts have always upheld fluoridation when considering this argument. Fluoride is a nutrient, and it is interesting that mandatory food supplementation with other nutrients, such as iodine, and vitamin D, have not engendered such passionate civil rights protests. It is useful to point out that the poor benefit most from fluoridation, since they generally have less adequate dental care. The rights of children should also be mentioned, since they derive a great deal of benefit from fluoride exposure when their teeth are developing, yet have no vote in a referendum. The Ontario committee[20] who reviewed the issue in 1961 said:

> xii. "We hold the firm opinion that the fluoridation of municipal water supplies by the authority of appropriate legislation would not be a denial of any fundamental or basic civil right or liberty which the Legislature of Ontario should protect and preserve."

Conclusion

In summary, water fluoridation has been the subject of a great deal of research and committee work which has drawn the conclusion that it is safe, effective, and cost-efficient. 1980 Canadian figures demonstrate clearly that there is a great deal more to be done in the implementation of this public health measure, however. Anti-fluoridationists have been very effective in pressuring local officials into eliminating fluoridation in their communities, or pushing for referenda, which frequently result in loss of fluoridation. As referenda become more common, communities which have been fluoridated for many years by order of the local council feel that its appropriate to hold a community vote on the subject. It is time that health professionals became more aggressive in promoting their stance, and took the initiative in seeing that unfluoridated communities acquire this type of primary dental prevention. Provincial governments could help greatly by amending current legislation to remove the bias against fluoridation. The federal government should become actively involved in promoting fluoridation in Canada. The scientific arguments in favour of fluoridation are now well established and the issue is in the political arena. If governments are truly concerned about prevention, here is a proven public health measure, inadequately applied, which they would do well to promote.□

REFERENCES

1. Berry, W.T.C. A study of the incidence of mongolism in relations to the fluoride content of water. *Am. J. Ment. Defic.*, 62: 634-6, Jan., 1958.
2. Brown, H.K., McLaren, H.R., Josie, G.H. and Stewart, BmA. The Brantford-Sarnia-Stratford fluoridation carries study-1955 report. *Canad. Dent. A.J.*, ww: 207-16, April, 1956.
3. Brown, H.K. and Poplove, M. Brantford-Sarnia-Stratford fluoridation caries study: final survey, 1963. *Canada. Dent. A.J.*, 31: 505-11, Aug., 1965.
4m Clark, D.Cm Water fluoridation in Canada: A status report 1980. *Canad. Dent. A.J.*, 47: supplement, Feb., 1981.
5.cClark, D.C. and Lang, W.P. Analyzing selected criticisms of water fluoridation. *Canad. Dent. A.J.*, 47:Supplement, Feb., 1981.
5. Clark, D.C. and Lang, W.P. Analyzing selected criticisms of water fluoridation. *Canad. Dent. A.J.*, 47: i-xii, March, 1981.
6. *Canadian Dental Association.* Fluoridation in Canada, December 31, 1970. Toronto, Ontario, 1971.
7. C.Da.A. Policy statement on controlled water fluoridation. *Canad. Dent. A.J.*, 47: supplement, Feb., 1981.
8. *Canadian Public Health Association.* Criteria document in support of a drinking water standard for fluoride. Ottawa, Ontario, 1979.
9. Dean, H.T. Epidemiological studies in the United States. In Moulton, F.R. (ed.): *Dental Caries and Fluorine.* Washington, D.C., American Association for the Advancement of Science, 1942, pp5-31.
10. *Department of National Health and Welfare, Canada.* Fluoridation and cancerG An analysis of Canadian drinking water fluoridation and cancer mortality data. No. 77:EHD-18, 1977.

Remaining extensive references available upon request.

On the Importance of Creativity In a Medical Education

Harley Hahn 8T4

There is a need for medical schools to coax and cherish creativity. Medical students ought to be the heirs of the great thinkers, synthesists, imagineers, creators, discoverers, and inventors of the past.

Imagine yourself visiting a medical school. What would you expect to see? Would you see groups of inspired men and women learning and discovering? Would it be a collection point for people interested in health, in bringing out the best in their fellows? Would the air vibrate with life and brilliance? After all, a medical school is a place where the brightest of the bright are trained to respect and honor life and to combat disease. Isn't it?

If you were to visit my school you would find boredom, fear, and discouragement. A mass of people who have learned how to "cope" rather than live. Are they happy? One look would tell you that the question is meaningless. From 9 to 5, and often for many other hours, these people are neighter happy nor sad; they are dull, humorless, and unimaginative. They are barely alive.

Visit the first year anatomy lab. See the rooms: each one the same complete with six dead bodies, twenty-four students in their white lab coats, and one instructor. Watch the students as they work; four to a group, each group dissecting the same part of the body at the same time.

Do they discover? Are they investigating the whys and hows of human bodies — the stuff of which they themselves are made? Look closely. Each group is following a set of green lab notes. Page after page, they are told what cuts to make, how to make them, and what to look for. The curiosity that has driven men to rob graves, to find out what lies under the skin, is nowhere to be found.

Let us visit a second year class. We find them in a large lecture hall equipped with all kinds of modern audio-visual machinery. See them sit, row after row, listening to a lecturer drone on and on. It is hard to tell who is more bored.

He shows a slide with a number of phrases written on it. The students copy them into their notebooks. The lecturer looks at the slide and talks off the top of his head. Dutifully, they take notes. (You never know what will be on the exam.) He shows another slide. They copy it down...and so, the long day wears on.

Clearly, much is wrong here. If nothing else, why are so many young minds wasted?

Let me describe my appreciation of what it means to be human. To me, it is more than being conscious and self-conscious; being human means being able to imagine. To create that which did not exist. To brood on sensations and facts and to invent a pattern. It is my imagination, my ability to manipulate abstract ideas and symbols, that affords me my sense of the past and of the future.

Young children are alive with excitment — imitation, discovery, experiment — and driven by curiosity. The drive to know *why* is, I believe, a fundamental one. The remarkable control that we have over our environment — from central heating in the winter to year-round fresh vegetables — stems directly from our curiosity. Our ability to ask, for example, what are the properties of steam? What would happen if I were to build a machine that generated steam under pressure? And most important: what could I do with such a machine?

This is the sort of curiosity and invention that we need in our medical schools. Our principal purposes are to study how people work and how to prevent and care for their illnesses. When we deny in ourselves those qualities that make us distinctly human, we lose something of the feeling for our art. The practise of medicine degenerates into lists of symptoms, diagnosis, and protocols of treatment.

***

Sometimes, if I'm quiet and I listen well enough, there is a voice. If I take off my stethoscope and relax I can hear it cry, like the deaf, dumb and blind boy in the opera Tommy: "SEE ME, FEEL ME, TOUCH ME, HEAL ME".

I listen to an old man tell me his medical history. What is he really saying? "I'm sorry. I'm sorry I smoked/drank/ate too much. It isn't my fault I got old. I don't want to die. I'm not sick, not ME. Who will help me? ME!"

And shush, quiet, I can hear: "see me, feel me, touch me, heal me". Yes, the voice. I can recognize it. It is mine.

***

What does the dullness and tension do to a medical student? It separates him from his patients

and from his species. Surely, That diseased artery in my pathology slide box can't be mine. Surely that dot on the far left side of the graph can't represent me. Will I too, one day, develop diabetes, cancer, heart disease? Somehow I doubt it. Anyway, old patients never die — they just come to autopsy.

But we lose more than our feelings for ourselves and our fellows. A dull confining education produces the traditional monkeys for us to carry on our backs: chauvinism and dogmatism. I am right and you don't know any better. What do I think about Vitamin C? I just don't believe in it.

It is no accident that the practise of medicine so often seems to be trying to decide what drug to give. Drugs are simple to prescribe, their use requires little imagination, and they are, for the most part, astonishingly non-toxic. How many potentially brilliant and artistic spirits have become mechanical pill pushers?

Our profession is lousy with chauvinism. But that is no stranger to the healing arts. I have met many an "alternative" doctor or practitioner who is as sure of his righteousness as he is of his neighbour's ignorance. As the saying goes, if you think you know all the answers, you haven't asked all the questions.

It is so easy to take ourselves too seriously, to mistake our efforts for a divine calling. I remember asking a surgeon friend of mine, what do you do if something important happens on the ward when you are operating? "Nothing is more important than surgery," he said. I persisted. What if someone has to interrupt you for something more important? "NOTHING," he repeated, "IS MORE IMPORTANT THAN SURGERY."

The problem, many people will cry, is science. Medicine has become too scientific. Students should spend less time learning science and more time studying human values and behaviour; as if ethics and psycology could serve as an antidote for an overdose of technical thought.

To me, this shows a fundamental misunderstanding of what science is and what it stands for. Science, actually, is a way of thinking. It is the practise that seeks to study and explain nature. And by "explain" I mean to impose patterns and theories on our understanding. For a scientist, the test of a theory is a simple one: does it work? Does it explain the observations?

What are the characteristics of a scientist? A scientist is skeptical. Of any assertion or theory, he asks: does it agree with the facts? If not, he refuses to accept the idea, no matter how tempting. A scientist is curious. He sees nature as intricate and fascinating, with properties to be discovered, appreciated and exploited. A scientist is artistic. He attends to detail and to pattern. From the yarn of experimentation, observation and reason, he weaves tapestries; each an image of nature, each more beautiful than the last.

I would like to end this eassy by reminding you of one of my earlier observations: that medical education wastes so many young minds. Most medical students are in their early twenties — an important age when ideas and beliefs are formed that must last a long time. Is it too late to fan the embers of imagination and wonder, rather to abandon them to slowly fade and die? My experience and my intuition say no.

One of my teachers recently remarked that if you see a medical students who invents a lot of theories you can be sure that he is either foolish or brilliant. Surely, we can do better than that.□

The University of Toronto Medical Alumni Association

B.I. Giblon, M.D.

Dr. B.I. Giblon, a Scarborough Family physician, graduated from the University of Toronto Medical School in 1957. He is also an attending staff of both the Scarborough General and Scarborough Centenary Hospitals. Dr. Giblon has been active in many professional societies and committees. He was the past president of the University of Toronto Medical Alumni Association and the Scarborough General Hospital Medical Society. Furthermore, he was the past representative on the University of Toronto Alumni College of Electors. Presently, he chairs the Scarborough branch of Ontario Medical Association and the Art Committee of Medical Alumni Association. As well, he serves as a member of Student aid, Finance and Update Committee of the Medical Alumni Association, and a member of the Undergraduate Medical Admissions Committe of the University of Toronto. Also, he is a member of the Convention Committee of the On tario Chapter, College of Family Physicians of Canada.

All graduates of the U of T Medical School are given free membership in the Medical Alumni Association (MAA) for one year, and are urged to maintain their membership by paying a small yearly fee, or by becoming a life member. Our Association date back to the old Federation which began in 1895 or 1896, but the present MAA was started in 1947. It originally was begun with the major purpose to raise funds for students, to assist with loans and bursaries toward the completion of studies. In recent years, the goals have broadened, and the alumni are involved to a greater and greater degree, not only in encouraging and assisting students, but also in recognition of teachers, serving on faculty committees, raising funds for special faculty projects, and representing the medical graduates on University graduate organizations, such as the College of Electors and the U of T Alumni Association. Since every undergraduate represents a future member of the organization, a brief outline of our present activities would be useful.

Funding for the MAA comes from three sources: there is a yearly membership fee, which pays for the cost of running the association; in addition, many members contribute a yearly donation for scholarship funds, or special funds; the third source of funds is from interest earned on previous donations. There is usually a surplus from the membership fees, and goes to support activities such as the Dean's Fund, contribution to the Medical Journal, the Arts and Letters Society, scholarship and literary prizes, as well as helping to organize the ongoing class reunions. Donations to the scholarship fund are used for scholarships and bursaries, summer student fellowships, transportation fund, fund for educational activities; special funds, such as Update, have assisted departments which are selected by the Dean, because of special needs. The undergraduate and postgraduate loan funds come from interest earned on investments, which were obtained mostly from bequests to the MAA. In addition, there are trust funds which were donated for specified awards to undergraduates or teachers in the Faculty.

Fees paid to the MAA are allocated to the various committees and fund a large variety of activities. The Art Committee works closely with Arts and Letters Society of the Medical Society, and has helped to sponsor Cultural Evenings, the Poetry and Prose Contest, the Photography Contest, the Doctors' Orchestra, and the Year Book. It encourages non-academic and cultural actitivities. The Graduation Banquet is entirely funded by the MAA, and is usually held in the Great Hall of Hart House, just after the completion of final year examinations or at the time of graduation. Invited guests are the graduating class as well as the fifty-year graduates, and MAA awards are usually presented at that time. The Graduate Magazine contains articles of interest, as well as news about our alumni and the graduating class. All alumni receive at least one issue per year, with paid-up members receiving

three. The Membership Committee contacts all graduates, informs them of activities, and encourages them to become members. The MAA has the highest participation rate of any alumni group of U of T. Honourary life medals are awarded to those individuals who have contributed "faithful service to the Association, outstanding teaching ability, special interest and influence upon the students, contribution to the progress of medicine in teaching or research, outstanding community service as a practicing physician, graduates who have made a pioneering contribution to the establishment of medical education in underdeveloped countries." The number of living Honourary Life Members is limited to 20. The office of the MAA is located in the Medical Science Building, and has one full-time employee, Mrs. Elizabeth Shenstone.

The donations and interest earned on investments are used by the Student Aid Committee to provide financial aid to students. Scholarships are awarded yearly to the top students of each year, selected by the Undergraduate Award Committee and the Alumni Student Aid Chairman. Similarly, the committee awards bursaries to students in need, as well as summer student fellowships. The MAA founded the summer student fellowship program, and presently gives 15 fellowships of $2000.00 each. Currently other organizations also contribute funding to this programme. The MAA Student Aid Committee also provides funds for the students' transportation fund (for electives), a fund for educational activities, and graduate bursaries. In addition, interest-free loans are made to undergraduates in need. The Student Aid Committee grants interest-fee loans from the Dalrymple Loan Fund in Psychiatry for post-graduate training in psychiatry. Also administered are the trust funds, which are set up for special awards. The Liz Gillespie Fund gives an award to the resident in psychiatry for the best paper in child psychiatry. The Dr. Delbert S. Hoare Fund is awarded to the two students who have contributed most to the continuing role of the MAA among the undergraduates of the Faculty of Medicine. The Dr. E. Mary Hollington Fund honours the two best teachers, chosen by the undergraduates. The Dr. Bernard A. Manace and Dr. L. Nelles Silverthorne Funds each provide student funds for a designated elective. The Dr. Robert P. Orange Memorial Fund provides an academic award and medal for academic excellence to a final year student. These and other trust funds are administered by the MAA without cost. The Update campaign was begun as part of the sesquicentennial anniversary of the Faculty. Since that time there has been an ongoing campaign, and the remaining funds will be used to help launch an ambitious fund initially planned to assist the Department of Nutrition. The Finance Committee is responsible for the investment portfolio,

(Continued on pg. 151)

par-ti´ci-pa´tion

"The state of being related to the larger whole."

In medicine in Ontario, it's the Ontario Medical Association that represents the larger whole. Comprehensive in membership — it unites the whole profession, gp's and specialists, practioners and students—comprehensive as well in its work, reflecting the profession's concern with clinical and scientific issues and with medical economics and politics, with practice management, and with the social questions that affect the professional and personal lives of today's physicians, the O.M.A. offers you participation.

For information on joing the Ontario Medical Association, simply write Anne Todd, Supervisor of Membership, O.M.A., 240 St. George Street, Toronto M5R 2P4; or phone 925-3264 (in Toronto), 1-800-268-7215 (toll-free outside Toronto).

Joining is only your first step in particpation

Ontario Medical Association

An Experiment in Ethics

To teach ethics or not to teach ethics, that was the very question which confronted a small group of students from the class of 8T4 who met in the fall of 1980 to reflect upon their early medical education. From their meeting emerged the perception that ethics was being 'taught', but in an irresponsible way: ethical positions were stated or implied, bandled about, and then dropped without the opportunity for dialogue or response. The group felt disatisfied with this state of affairs, and they resolved to do something about it. That something was the medical ethics elective, 1980-81.

Last year the elective consisted of seven one-hour lunchtime sessions (each followed later by one hour of small group discussion), covering such topics as "Ethics, Values and Socialization in Medical School", "Patients' Rights", "Artificial Life and the Right to Natural Death", and "Clinical Trials and Human Experimentation". Speakers were physicians, philosophers and lawyers. Eighty students completed the elective; their comments were so encouraging that it was decided the elective would continue.

To improve on the previous year's effort, a new student organizing committee met through the summer of 1981 to begin designing a more unified and comprehensive program. To this end, they recruited the aid of Prof. Abbyann Lynch, a philosopher and ethicist from St. Michael's College. The result is this year's medical ethics elective.

The 1981-82 series consists of twenty-five one-hour lunchtime sessions. Six broad topic areas are dealt with: truth and consent, medicine and power, humans in teaching and experimentation, medicine and special interest groups (e.g. the handicapped, the elderly), women and medicine, and physicians and social responsibility. Speakers have been physicians, philosophers, lawyers, and representatives of public specialal interest groups. One hundred and twenty students from 8T4 and 8T5 are regularly attending these sessions.

To ask whether ethics should be taught in medical school is to ask a moral question. One way to judge an action is by its consequences. We submit that showing one hundred and twenty physicians-to-be how to recognize and reflect upon moral issues is a beneficial consequence. □

Paul Ferner 8T4
Peter Singer 8T4

(Continued from page 140)

computer, for a machine may soon be able to perform satisfactory histories and physicals. If medical students do not develop human qualities as applied to medicine early in their training, then they are taking the risk of throwing their profession into the same league as the condition of smallpox. But this is another topic for discussion. □

Acknowledgement:

I would like to thank Dr. J. Crookston of TGH for showing me that lectures and essays need not be dry, ivory-tower types of presentations.

(Continued from page 150)

meeting three times a year to review the various investments held by the MAA, and advises changes in the portfolio. The Life Membership Fund is the accumulation of monies paid by the alumni for life membership, presently $300.00. The fund is kept in perpetuity, with the interest credited toward MAA operating expenses.

The MAA sends two representatives to the U of T Alumni Association, which represents all the Faculties and Colleges. There are also two representatives on the U of T College of Electors, one on the Varsity Fund Board, two on the Medical Faculty Council, and one on the Undergraduate Medical Admissions Committee.

I would like to thank Mrs. E. Shenstone for supplying an outline, as well as information contained in this article. □

PATRONS

Each year a number of our supporters donate an amount well above and beyond the mere subscription rate. For their generous financial support (with its consequent psychological boost) we would like to extend our sincere thanks to the following individuals.

Dr. P.W. Alberti, Toronto
Dr. E.C. Allen, Toronto
Dr. K.A. Ally, Agincourt
Dr. Ulo Ambus, Toronto
Dr. Crawford S. Anglin, Toronto
Dr. John G. Ashby, Montreal
Dr. Mary Jane Ashley, Toronto
Dr. Michael A. Baker, Toronto
Dr. M.B. Bardenstein, Michigan
Dr. Eric Barker, Wiarton
Dr. T.W. Barrington, Don Mills
Dr. C.E. Bayliss, Toronto
Dr. Patrick F. Beirne, Toronto
Dr. Sam Berger, Toronto
Dr. John A. Beswick, West Hill
Dr. Charles B. Brown, Toronto
Dr. Martin Buckspan, Toronto
Dr. David S. Byers, Toronto
Dr. Paul A. Cameron, Toronto
Dr. A. Cecutti, Don Mills
Dr. Abraham Chaiton, Downsview
Dr. Albert T. Cheskes, Toronto
Dr. Sheila Cohen, Willowdale
Dr. D. H. Cowan, Toronto
Dr. John S. Crawford, Toronto
Dr. D. A. Davidson, Weston
Dr. Yvonne E. De Buda, Toronto
Dr. R.B. Disenhouse, Willowdale
Eli Lilly Canada Inc., Scarborough
Dr. J. Duffin, Toronto
Dr. Robert E. Ecclestone, Oakville
Dr. Emmanuel Farber, Toronto
Dr. Shim Felsen, Willowdale
Dr. Mary K. Ferriman, Toronto
Dr. Ross Fleming, Toronto
Dr. Rodney S. Fowler, Toronto
Dr. Robert W. Francis, Toronto
Dr. W.H. Francombe, Toronto
Dr. John Fredrickson, Toronto
Dr. Aruis Freiberg, Toronto
Dr. Ivan I.V. Gartha, Toronto
Dr. A. Geisler, Mississauga
Dr. R.M. Gladstone, Willowdale
Dr. David M. Goldberg, Toronto
Dr. Irvin Gollish, Toronto
Dr. P. Goodhall-Gunn, Islington
Dr. Allans Gordon
Dr. Duncan A. Gordon, Toronto
Dr. C. C. Gray, Toronto
Dr. Allen E. Gross, Toronto
Dr. L. F. L. Grover, Islington
Dr. A. L. Halpern, New York
Dr. Edward S. Hamer, Toronto
Dr. Ian Harrington, Don Mills
Dr. Gerald D. Hart, Toronto
Dr. R. D. Henderson, Toronto
Dr. Robert C. Hicks, Toronto
Dr. F. Marguerite Hill, Toronto
Dr. M. A. Hutcheon, Toronto
Dr. Aden C. Irwin, Halifax
Dr. Mary V. Jackson, Toronto
Dr. D. P. Jones, Toronto
Dr. James H Kerr, Toronto
Dr. E. C. Keystone, Toronto
Dr. J. S. Keystone, Toronto
Dr. H. King, Midland
Dr. Cecilia Lamenza, Toronto
Dr. Bernard Langer, Toronto
Dr. Eugene LeBlanc, Toronto
Dr. Jack R. Leitch, Toronto
Dr. Daniel Levy, Hamilton
Dr. Joseph Huggins, Don Mills.
Dr. Kenneth E. Livingston, Toronto
Dr. E. Llewellyn-Thomas, Toronto
Dr. L.F.W. Loach, Toronto
Dr. Frederick Lowy, Toronto
Dr. John R. Lundon, Toronto
Dr. Ross C. Mackay, Toronto
Dr. Robert Mackenzie, Toronto
Dr. Ian Macnab, Toronto
Dr. C. Mallin, Toronto
Dr. J.T. Marotta, Don Mills
Dr. A. Bruce Marshall, St. Marys
Dr. Benj. Massouda, Downsview
Dr. Rebeka Moscarello, Toronto
Dr. James F. Murray, Don Mills
Dr. R. W. McCallum, Agincourt
Dr. Raymond M. KcKeown, Oregon
Dr. F. R. Papsin, Toronto
Dr. G. A. Pengelly, Willowdale
Dr. Richard G. Perrin, Toronto
Dr. Walter J. Peters, Toronto
Dr. Mel. E. Petersiel, Scarborough
Dr. Burns Plewes, Toronto
Dr. C. P. Rance, Toronto
Dr. W. J. Reynolds, Toronto
Dr. Alexander Roberts, Toronto
Dr. Robert B. Salter, Toronto
Dr. E. A. Sellers, Toronto
Dr. Isaac H. Shleser, Toronto
Dr. Jack Shuber, Toronto
Dr. Ruth Sky, Toronto
Dr. A. & J. Smith, Mississauga
Dr. D. A. Stewart, Toronto
Dr. R. M. Stone, Toronto
Dr. M. Tile, Toronto
Dr. Joan M. Vale, Toronto
Dr. Daniel G. Vaughan, California
Dr. Paul G. Walfish, Toronto
Dr. Gary Webb, Toronto
Dr. K. Weber, Toronto
Dr. Douglas R. Wilson, Toronto
Dr. J. K. Wilson, Toronto
Dr. George E. Wodehouse, Toronto
Dr. M. S. Wolochow, Vancouver
Dr. C. R. Woolf, Toronto
Dr. J. R. Wright, Toronto
Dept. of Surgery, U. of Toronto
Governing Council, U of Toronto

MEDICAL ETHICS CONTEST

The Journal regrets to announce that due to poor response, the recent Medical Ethics Essay Contest was cancelled.